CLINICAL STUDY PROTOCOL

ATLAS

ICTU ADOPTED

Full Study Title:
A randomised controlled trial of regular MRI scans compared to standard care in patients with prostate cancer managed using active surveillance

Short Study title / Acronym:
Imperial Prostate 9 – ATLAS (**A**pproaches **T**o **L**ong-Term **A**ctive **S**urveillance)

Sponsor:
Imperial College London

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This protocol describes the IP9-ATLAS 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 Frame Work 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 (AMEND AS NECESSARY)

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EPIC	Expanded Prostate Index Composite
HRA	Health Research Authority
HADS	Hospital Anxiety and Depression Scale
ICHNT	Imperial College Healthcare NHS Trust
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
ITT	Intention to Treat
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
MRI	Magnetic Resonance Imaging
NICE	National Institute for Health and Care Excellence
PET	Positron Emission Tomography
PI	Principal Investigator
PROMS	Patient-reported Outcome Measures
PSA	Prostate Specific Antigen
RCT	Randomised Controlled Trial

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TRIAL SUMMARY

TITLE	A randomised controlled trial of regular MRI scans compared to standard care in patients with prostate cancer managed using active surveillance
OBJECTIVES	**Primary Objective** In patients on active surveillance for prostate cancer, to demonstrate that use of regular MRI scans is better able to detect cancer progression over 5 years compared to the current NICE defined strategy. **Secondary Objectives** - To carry out an economic evaluation to determine the cost-effectiveness of revising the prostate cancer active surveillance protocol to incorporate regular surveillance MRI. In each randomised group to measure, - Compliance to allocated surveillance strategy - Patient reported outcome measures on urinary, sexual and bowel function; cancer-related anxiety; and overall health-related quality of life - Proportion undergoing biopsy - MRI and biopsy-related side-effects and complications - Proportion treated, and types of treatment (surgery, radiotherapy, focal therapy) in patients with or without progression
DESIGN	Two-arm randomised controlled trial
SAMPLE SIZE	1,263 participants will be randomised to allow for 5% loss to follow-up.
INCLUSION AND EXCLUSION CRITERIA	*Inclusion* - Age 18 years or above (no upper limit) - Patients with a prostate (either cis-male gender or trans-female gender with no prior androgen deprivation hormone use at all). - - Diagnostic systematic biopsy +/- targeted biopsy - A histological diagnosis of localised prostate cancer - Patient chosen active surveillance *Exclusion* - On active surveillance for greater than 9 months prior to screening date. - Contraindication to MRI or gadolinium contrast - Previous hip replacement to both hips - Contraindication to performing a biopsy guided by a transrectal ultrasound probe
MAIN STUDY PROCEDURES	Current (NICE defined active surveillance): PSA will be 3 monthly with rectal exam annually, if clinically indicated. MRI will be carried out at 12 months (if not had one at diagnosis). If a diagnostic MRI was carried out, a 12 month MRI scan will not be required. A biopsy will be required if indicated due to changes in rectal

	exam or PSA (PSA doubling time < 3 years). Changes in PSA will be determined by PSA doubling time, which should be calculated every 6 months (https://www.mskcc.org/nomograms/prostate/psa_doubling_time). Follow-up for 5 years. Intervention (Regular MRI based active surveillance): Patients with a visible lesion or medium risk cancer (Grade Group 2) will have PSA 6 monthly and MRI annually. As per international PIRADS committee guidance the surveillance MRIs will be biparametric MRI scans which last approximately 15 minutes and exclude gadolinium contrast injection. Patients with a non-visible lesion and low risk cancer (Grade Group 1) will undergo PSA 6 monthly and MRI in years 1, 3 and 5. In all patients, a targeted biopsy will be carriedout if the MRI PRECISE v2.0 score is >/=4.
OUTCOME MEASURES (PRIMARY ENDPOINTS)	Progression in each group defined as higher risk cancer on biopsy (Grade Group >/=3) or higher stage (>/=T3 or >/=N or >/=M1) over 5 years Prostate cancer progression rates and time to progression in each randomised arm defined on, • biopsy: grade progression to Grade Group 3 or greater or detection on biopsy of intraductal cancer or lymphovascular invasion. Many of our clinicians would include patients on active surveillance with cribriform pattern on Grade Group so this is not a factor for progression. • staging: cancer has spread to surrounding tissues (extracapsular), lymph node involvement or distant body parts as demonstrated on cross-sectional imaging including MRI, CT, bone-scan or PET scans as deemed appropriate by the local multidisciplinary cancer team.
OUTCOME MEASURES (SECONDARY ENDPOINTS)	- Cost-effectiveness of revising the prostate cancer active surveillance protocol to incorporate regular surveillance MRI - Proportion of patients requiring biopsy - MRI & biopsy-related adverse events - Type of treatment for patients who progress and those who do not progress (prostatectomy, radiotherapy, brachytherapy, focal therapy) - Type of treatment for lower urinary symptoms for patients who progress and those who do not progress - Use of systemic therapy and type in those who progress and those who do not progress - Compliance measured as proportion having each test (PSA, rectal exam, MRI) at each allocated timepoint and proportion agreeing to a biopsy when clinically recommended - Annual changes in PROMS using validated questionnaires, compared to baseline, to measure impact on urinary, erectile and bowel function (EPIC) as well as cancer-related anxiety (HADS),and overall health-related quality of life (EQ-5D-5L) - Inter-observer variability in reporting surveillance MRI scans in the MRI group

	Longer-term follow-up All patients will be consented for linkage to national databases. Clinical outcomes can be collected after study end on use of subsequent tests and treatments as well as adverse events and survival.

1. BACKGROUND

1.1 Clinical setting

Our research question is the following:

P - In patients who have chosen active surveillance following a diagnosis of localised prostate cancer,

I - is the use of regular MRI scans

C - compared to current NICE defined active surveillance,

O - better at detecting cancer progression (biopsy evidence Grade Group >/=3 OR stage >/=T3 OR >/=N1 or >/=M1) with less cost to the NHS (fewer PSA tests, biopsies and clinic visits)?

What is the problem being addressed?

Of 5 research priorities that NICE have identified for prostate cancer, two relate to improving active surveillance [1]. Similarly, the James Lind Alliance has 3 research priorities to improve active surveillance [2]. Of 50,000 newly diagnosed patients with prostate cancer every year, about 7,600 choose active surveillance rather than immediate surgery or radiotherapy [3-5]. Most have low risk (70-80%) whilst 20-30% have medium risk prostate cancer [6]. This is because low and medium risk prostate cancers grow slowly [7]. As a result, immediate treatment does not improve cancer-specific survival over 10 years [8] but can cause significant urinary, sexual and bowel side-effects [9,10]. Given this fact, it is important that patients suitable for active surveillance have confidence in choosing it [11]. Our recent discrete choice experiment (COMPARE) study of 740 newly diagnosed patients with localised prostate cancer showed that patients were willing to prioritise active surveillance so as to avoid the impacts of radical therapy and even accept slight detriments in cancer control to do so [12].

Although these cancers are generally slow growing, nevertheless 25-34% will progress to higher risk cancer over 5 years and subsequently need treatment. Whilst the long-term data describing the effects of delayed detection of progression on survival are maturing, a recent systematic review has shown detrimental effects on other important aspects of cancer control [13], including metastasis which has been shown to be a validated surrogate for cancer related mortality [14]. For instance, in the largest RCT comparing active surveillance

to immediate surgery or radiotherapy, 2.4 times as many patients had disease progression and cancer spread to other parts of the body in the active surveillance arm [8]. So, active surveillance needs to be improved.

The UK NICE guidelines currently advise that active surveillance should involve regular prostate specific antigen (PSA) blood tests and rectal examinations. They advise an MRI within 12-18 months if the patient did not previously have an MRI (a scenario which is increasingly unlikely in the UK due to a new NICE recommendation in 2019 incorporating an MRI for diagnosis before first biopsy) [1]. After one year, NICE advise regular PSA and rectal examination and for doctors to decide when further tests should be done. PSA and rectal examination changes are inaccurate in predicting progression. As a result, some centres do repeat regular biopsies every 1-2 years [15]. However, biopsies on their own are inaccurate as they are ultrasound-guided, so the operator can see the prostate but not areas that are suspicious for cancer progression. As a result, biopsies sample the whole prostate in a random manner in the hope of hitting the cancer. Biopsies also have side-effects such as infection/sepsis, bleeding and pain [16] and when these occur, patients are less likely to agree to further biopsy [17]. Biopsies cost £488 and lead to significant NHS resource use. Regular and repeat biopsies can also cause scarring around the prostate making any subsequent surgical treatment more difficult [18] with impacts on erectile function [19,20]. Whilst there is no evidence of that delayed detection of progression has an impact on survival, a recent systematic review has shown deleterious effects on other aspects of cancer control [21]. NICE currently advise that active surveillance should involve 3-6 monthly prostate specific antigen (PSA) blood tests and rectal examinations. They advise an MRI and biopsy at 12 months [1]. After one year, 3-6 monthly PSA and rectal examinations are recommended and further biopsy if the PSA starts to rise or if the rectal exam detects a prostate nodule. This is problematic for 3 reasons:

First, PSA and rectal examination changes are inaccurate in detecting progression. As a result, some centres do regular biopsies every 1-2 years; this is borne out by our 48 physician survey (Jan 2022). However, biopsies alone are also inaccurate as they are ultrasound-guided; the operator can see the prostate but not areas suspicious for cancer progression. Second, biopsies have side-effects such as infection, bleeding and pain; when these occur, patients are less likely to agree to further biopsies. Third, 10-43% of patients often decide to have treatment even if the cancer has not progressed. This is because of anxiety about living with cancer [22], or because of the biopsy and burden of tests [23,24]. Some studies have shown other psychological impacts such as sub-clinical depression, illness uncertainty and hopelessness [25,26].

We propose using regular MRI scans in active surveillance to detect progression. Our team led the pivotal UK studies which changed recommendations for MRI in diagnosing prostate cancer [27,28]. Subsequently, we and others have shown that regular prostate MRI scans with targeted biopsies to areas of suspicion are accurate in ruling-out and detecting progression [29,30]. To change NHS practice, an RCT is needed to compare regular MRI scans to current NICE defined standard of care in patients who choose active surveillance following an MRI-directed biopsy at time of diagnosis. Our proposal was positively reviewed by the NCRI Prostate Proposal Guidance panel (7/2/2022).

1.2 Intervention details

(i) Clinical studies

Current active surveillance

Currently NICE recommends regular PSA measurement and rectal examinations but does not define what type of changes should trigger further investigations. Metrics such as PSA doubling time and PSA velocity are often used but the literature demonstrates that PSA doubling time changes are not, and PSA velocity only weakly, associated with progression [32-37]. NICE also admit there is scarcity of data supporting regular rectal examinations but as this is included in most active surveillance studies, they do recommend its use. There is some limited evidence that rectal examinations may be useful in predicting progression [38]. The sensitivity of rectal exam in predicting progression in 2029 patients on active surveillance was shown to be in the range of 32% to 37% [39]. The sensitivity and specificity of PSA kinetics in predicting progression on biopsy has been shown to be 40-59% and 44-78%, respectively [40].

PSA increases on active surveillance are weakly associated with progression, with sensitivity of 40-59% and specificity of 44-78%, respectively. NICE also state there is scarcity of data supporting regular rectal examinations but as this is included in most active surveillance studies, they recommend its use. Rectal examinations have sensitivity of 32-37% in predicting progression (specificity not reported) [34].

The European Association of Urology guidelines (2023) (https://uroweb.org/guidelines/prostate-cancer/chapter/treatment) state that:

- Base follow-up during active surveillance (AS) on a strict protocol including digital rectal examination (at least once yearly), prostate-specific antigen (PSA) (at least once every 6 months) and repeated biopsy every 2 to 3 years.
- Perform magnetic resonance imaging (MRI) and repeat biopsy if PSA is rising (PSA-doubling time < 3 years)

Regular MRI in active surveillance

Two RCTs evaluated the role of an early MRI within the first year of active surveillance. The ROMAS RCT [41] followed up to only 12 months (2015-2018). 124 patients were initially diagnosed without MRI and then randomized to have an early confirmatory MRI and biopsy at 3 months followed by a further 12-core systematic biopsy at 12 months. The control group underwent 12-core random biopsy at 12 months. They showed that by doing an early MRI at 3 months many important cancers missed at the time of diagnostic systematic biopsy were picked up so that there were fewer of these cancers subsequently detected at 12 months. The updated 2-year 259 patient follow-up data from the ASIST RCT in Canada also similarly evaluated the role of a confirmatory MRI-directed biopsy carried out within 3-6 months of a patient choosing active surveillance when diagnosed using a systematic biopsy without MRI. Subsequent MRI scans were not performed routinely [42,43]. ASIST showed fewer downstream cases progressing in the confirmatory MRI (19/98, 19%) compared to the standard care group (35/101, 35%; p=0.017); 2-yr biopsy outcomes were 9.9% (8/81) for confirmatory MRI and 23% (17/75) for standard care; p=0.048). Critically, significant

differences in failure rates were detected across the 3 centres in the confirmatory MRI arm (4.2% [2/48] vs 17% [4/24] vs 27% [7/26]; p=0.019) indicating the importance of centre expertise.

Critically, the RCTs did not evaluate the role of surveillance MRI scans after the first year. Rather they evaluated the role of an early confirmatory MRI with biopsy to overcome the initial inaccuracy of a systematic biopsy, so have less relevance to UK practice. This is because in the UK practice has changed to doing an initial diagnostic MRI before first biopsy [NICE guidelines, 2019].

Five systematic reviews on the role of MRI in active surveillance have been conducted in the last 6 years including 800 to 6605 patients. These have shown pooled sensitivities of 59%, 61%, 74%, 79% and 81%; studies using stringent criteria on biopsy (as we propose in our RCT) show higher sensitivities. Specificity was 75%, 76%, 78%, and 81% (one did not report). Negative predictive values were in the range 75%-94% indicating patients could safely avoid repeat biopsies if the MRI shows no progression.

Guo et al (2015) [44] evaluated 6 studies with diagnostic accuracy of MRI for disease reclassification among active surveillance patients. They showed a sensitivity of 0.74 (95%CI 0.45–0.91) and specificity 0.81 (95%CI 0.56–0.94). In addition, when no suspicious disease progression (66%) was identified on MRI, the chance of finding progression on repeat biopsy was extremely low at 6%. Cantiello et al (2019) [45] had a much broader entry criteria for their meta-analysis including 43 studies with a total of 6,605 patients. They showed 1.5 Tesla MRI had sensitivity of 0.60 and NPV 0.75 and for 3.0 Tesla MRI a sensitivity of 0.81 and NPV 0.78.

Hettiarachchi et al (2020) [46] evaluated 7 studies with 800 patients. The pooled pathological progression rate was 27%. The pooled sensitivity and specificity of MRI for disease progression were 0.61 (95%CI 0.46–0.74) and 0.78 (95%CI 0.54–0.91), respectively. Adjusting for a prevalence of disease progression of 30% resulted in a PPV 0.43 (95% CI: 0.39–0.46) and NPV of 0.81 (95% CI: 0.78–0.84). They observed significant heterogeneity.

Baccaglini et al (2020) [47] conducted a meta-analysis of 6 studies enrolling 741 patients. The pooled sensitivity for MRI with targeted biopsy of suspicious areas was 0.79 (95%CI, 0.74-0.83) and 0.67 for systematic biopsy alone (95%CI 0.63-0.74). They did not report specificity.

Finally, Rajwa et al (2021) [48] included 15 studies with 2240 patients. Six used PRECISE criteria [49] and nine institution-specific definitions of MRI progression. The pooled progression rate, which included histological progression to ISUP Grade Group ≥2, was 27%. The pooled sensitivity and specificity were 0.59 (95%CI 0.44-0.73) and 0.75 (95%CI 0.66-0.84), respectively. There was significant heterogeneity between included studies. Depending on prevalence of progression, the pooled NPV for serial prostate MRI ranged from 0.81 (95%CI 0.73-0.88) to 0.88 (95%CI 0.83-0.93) and the pooled positive predictive value ranged from 0.37 (95%CI 0.24-0.54) to 0.50 (95%CI 0.36-0.66). When using a more robust definition of histological progression (ISUP GG >/=3), the performance was better: sensitivity 0.695 (95% CI 0.465–0.925), specificity 0.619 (95% CI 0.446–0.793), PPV 0.134 (95% CI 0.059–0.209), NPV 0.954 (95% CI 0.907–0.100).

Standardised reporting of surveillance MRI scans

The Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) scoring system was developed by some of our group as part of an international

consortium to standardise the reporting of surveillance MRI scans [50-52]. A 5-point ordinal scale was developed to determine what constitutes a clinically significant change on MRI. A score >/=4 shown to accurately rule-out and detect progression. A number of studies have subsequently validated the role of PRECISE scoring showing good performance characteristics in ruling-out and detecting progression [52-57] with the latest UK data showing sensitivity, specificity, PPV and NPV of 74.1% (95%CI 57.5–90.6), 94.7 (95%CI 87.6–1), 90.9% (95%CI 78.9–1), 83.7% (95%CI 72.7–94.8), 84.4% (95%CI 72.6–96.2), respectively [58]. There is also substantial inter-rater agreement [59]. This system has been shown, when taught through a dedicated teaching course once, significantly improve accuracy of assessment of radiological change in serial prostate MRI in the average area under the curve (AUC) from 0.60 [95% CI 0.51-0.69] to 0.77 [95% CI 0.70-0.84]) (p = 0.004).

Some of our group, as part of an international consortium, developed and validated a 5-point ordinal scoring system called Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE). This standardised the reporting of surveillance MRI [35-37]. Studies have shown good accuracy for detecting progression [38-40]. Sensitivity, specificity, PPV and NPV were 74%, 95%, 92%, 84%, respectively [41] with good inter-rater agreement [42].

Rates of MRI reported change as indicated by a PRECISE score of 4 or greater was 22% of patients with median follow-up 52 months (IQR 35-68) (Cambridge) and 43% (UCL) with median follow-up 76 months (IQR 52-100.5). Only 4/309 (1.3%) in the Cambridge series and 1/672 in the UCL series left the AS programme due to patient choice.

Progression rates

A number of studies have shown progression rates using MRI in surveillance in the modern diagnostic era where a baseline MRI or confirmatory MRI was carried out. 5-year outcomes from 519 patients undergoing surveillance MRI scans from two US centres showed progression to Grade Group >/=2 of 31.6% and Grade Group >/=3 in 17.7% [60] with those having a cancer from an MRI-targeted biopsy much more likely to progress. An Italian group has shown progression of 91 (25%) and 21 patients (5.8%) experienced ISUP GG≥2 with >10% of pattern 4 and ISUP GG ≥ 3, respectively in 588 patients over a median of 3 years follow-up [61]. Our UK cohort of 672 patients on active surveillance over a median of 5-6 years showed progression to requirement of treatment of about 30% [62,63]. The PRIAS consortium has recently shown reclassification rates at the first biopsy while on AS is similar between patients diagnosed with and without upfront MRI (23% to GG ≥2 and 7% to GG ≥3 vs 19% and 6%, respectively) [64].

A recent 2022 systematic review focusing on comparing risk of progression with intermediate versus low-risk disease included 25 studies with 29,673 unselected intermediate risk patients [65]. The 10-yr treatment-free, metastasis-free, cancer-specific, and overall survival ranged from 19.4% to 69%, 80.8% to 99%, 88.2% to 99%, and 59.4% to 83.9%, respectively. IR patients had similar treatment-free survival to LR patients (risk ratio [RR] 1.16, 95% confidence interval (CI), 0.99–1.36, p = 0.07), but significantly higher risks of metastasis (RR 5.79, 95% CI, 4.61–7.29, p < 0.001), death from prostate cancer (RR 3.93, 95% CI, 2.93–5.27, p < 0.001), and all-cause death (RR 1.44, 95% CI, 1.11–1.86, p = 0.005). In a subgroup analysis of studies including patients with GG ≤2 only (n = 4), treatment-free survival (RR 1.03, 95% CI, 0.62–1.71, p = 0.91) and metastasis-free survival (RR 2.09, 95% CI, 0.75–5.82, p = 0.16) were similar between low risk and intermediate risk

patients. Treatment-free survival was significantly reduced in subgroups of patients with unfavourable intermediate disease and increased cancer length on biopsy.

Overall cancer progression rates during active surveillance in the modern diagnostic era are 27-34% over 5 years [43-47].

1.3 Rationale for the study

a) The regular use of MRI in active surveillance will lead to greater confidence in active surveillance for patients with low and medium risk prostate cancer. This is because such a strategy is likely to detect cancer progression earlier with fewer invasive biopsies [31]. In our studies, <2% patients chose treatment during surveillance due to anxiety (UCL and Cambridge).

b) An additional ~2000 patients with medium risk cancer could be managed with active surveillance in future [3]. This is because there is currently reluctance to monitor particularly those patients who have intermediate grade group to disease due to a concern about progression. Both patient and physician confidence will increase if there is a robust strategy for monitoring that can detect progression earlier than current practice.

c) Fewer NHS resources for clinic follow-ups, PSA tests and biopsies. With regular and routine imaging follow-up we anticipate that there should be fewer clinical reviews in hospital and fewer PSA blood tests and as a result of our study outcomes if MRI is shown to be a robust strategy for follow up then routine biopsy can also be avoided and thus avoid the toxicity of those biopsies and the fact that such biopsies add both burden to patients and healthcare systems and can often lead to patients deciding on treatment even though the cancer shows no sign of progression. Our own data shows that patients on routine regular MRI scans are more likely to stay on surveillance with one percent or less deciding to come off surveillance even though the disease is not progressing.

Our study was reviewed by the NCRI panel in February 2022. The feedback was very positive and the proposal was strongly supported. The panel gave critical feedback in how to improve the proposal in terms of radiological and biopsy standardisation and ensuring patient education within the trial material. They also asked that we provide guidance to centres on a standardised approach to the control arm and ensure compliance. NCRI asked that we ensure wide representation but not include unfavourable intermediate risk disease. We have explained this in our section on eligibility criteria.

1.4 Risk / Benefit Assessment

Patients participating in this study will continue on their standard care pathway with monitoring, so will not be at risk of progression not being detected. Those patients randomised to the intervention arm will have additional MRI scans. These will be non-contrast so there is no risk from having repeated 1-2 yearly injections of gadolinium contrast. Patients with contraindications to MRI will not be taking part in the study so will not be exposed to an unnecessary MRI.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

In patients on active surveillance for prostate cancer, to demonstrate that use of regular MRI scans is better able to detect cancer progression over 5 years compared to the current NICE defined strategy.

2.2 Secondary Objective

- To carry out an economic evaluation to determine the cost-effectiveness of revising the prostate cancer active surveillance protocol to incorporate regular surveillance MRI.

In each randomised group to measure,
- Compliance to allocated surveillance strategy
- Patient reported outcome measures on urinary, sexual and bowel function; cancer-related anxiety; and overall health-related quality of life
- Proportion undergoing biopsy
- MRI and biopsy-related side-effects and complications
- Proportion treated, and types of treatment (surgery, radiotherapy, focal therapy) in patients with or without progression

2.3 Primary Endpoint

Progression in each group defined as higher risk cancer on biopsy (Grade Group >/=3) or higher stage (>/=T3 or >/=N or >/=M1) over 5 years.

Prostate cancer progression rates and time to progression in each randomised arm defined on,

- biopsy: grade progression to Grade Group 3 or greater or detection on biopsy of intraductal cancer or lymphovascular invasion. Many of our clinicians would include patients on active surveillance with cribriform pattern on Grade Group so this is not a factor for progression.
- staging: cancer has spread to surrounding tissues (extracapsular), lymph node involvement or distant body parts as demonstrated on cross-sectional imaging including MRI, CT, bone-scan or PET scans as deemed appropriate by the local multidisciplinary cancer team.

2.4 Secondary Endpoints

- Cost-effectiveness of revising the prostate cancer active surveillance protocol to incorporate regular surveillance MRI
- Proportion of patients requiring biopsy
- MRI & biopsy-related adverse events
- Compliance measured as proportion having each test (PSA, rectal exam, MRI) at each allocated timepoint and proportion agreeing to a biopsy when clinically recommended
- Annual changes in PROMS using validated questionnaires, compared to baseline, to measure impact on urinary, erectile and bowel function (EPIC) as well as cancer-related anxiety (HADS), and overall health-related quality of life (EQ-5D-5L)

- Inter-observer variability in reporting surveillance MRI scans in the MRI group

Longer-term follow-up
All patients will be consented for linkage to national databases. Clinical outcomes can be collected after study end on use of subsequent tests and treatments as well as adverse events and survival.

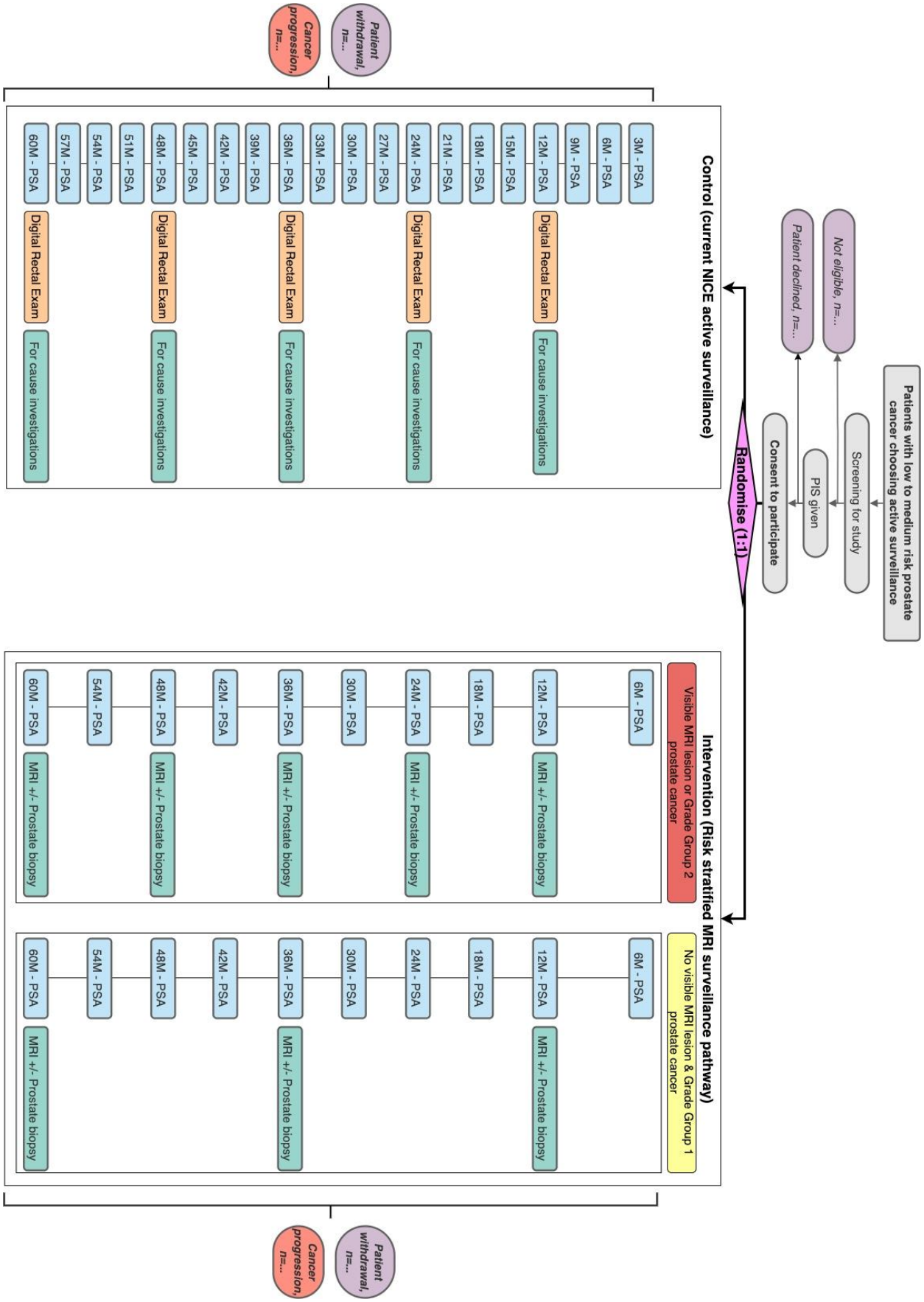
2.5 Summary Table of Objectives and Endpoints

Objectives	Endpoints	Timepoint(s) of evaluation of this endpoint (if applicable)
Primary Objective	As above	5 years
Secondary Objectives	As above	5 years

3. STUDY DESIGN

A multicentre, RCT allocating patients in a 1:1 ratio to either regular MRI scans or the current NICE defined standard, with embedded trial and model based economic evaluation. Randomisation will be blocked (random block size) not blinded to participants (effectively open-label) and stratified by MRI visibility of lesion (3 categories [no visible lesion, diffuse changes, discrete visible lesion]), cancer Grade Group (GG1, GG2) and time since diagnosis.

3.1 Flowchart



4. PARTICIPANT ENTRY

4.1 Study setting and population

Patients with a histological diagnosis of localised prostate cancer in the 9 months prior to screening visit who have chosen active surveillance. Nine months was chosen following advice from our focus groups to include patients diagnosed as close to 1 year prior to screening as possible to maximise participation as they felt this study would be very popular for men on active surveillance.

(i) Inclusion criteria

- Age >/= 18 years
- Diagnostic systematic biopsy +/- targeted biopsy. We will permit, in a pragmatic manner, any number of targets and any number of systematic biopsies and we will also permit either transperineal or transrectal biopsies. In the UK, 2-3 years ago, 60% of centres were carrying out transperineal biopsy and we anticipate by the time we start our study, the vast majority of centres will be carrying out transperineal targeted and systematic biopsies following a standard protocol equivalent to Ginsberg or the RAPID protocol. This is the approach we have taken in our multi-centre prospective randomised controlled trial called IP7–PACIFIC funded by Cancer Research UK [66].
- A histological diagnosis of localised prostate cancer staged using a pre-biopsy prostate MRI. Grade Group attribution will be based on an overall assessment of all positive cores and not on the maximal grade in any one core, which is standard UK practice. Recently, NICE have adopted the CPG vacation criteria and have recommended that patients in CPG groups 1, 2 and 3 can be offered active surveillance. These two groups approximate to the previous low and medium risk strata but exclude men who have unfavourable intermediate risk disease who the majority of clinicians would not offer active surveillance to, due to the significant risk of progression of disease and subsequent higher risk of disease failure following treatment. The CPG 1 includes Gleason score 3+3=6 (grade group 1) and prostate-specific antigen (PSA) less than 10 microgram/litre and Stages T1–T2. CPG 2 includes Gleason score 3+4=7 (grade group 2) or PSA 10 microgram/litre to 20 microgram/litre and Stages T1–T2. CPG 3 includes Gleason score 3+4=7 (grade group 2) and PSA 10 microgram/litre to 20 microgram/litre and Stages T1–T2 or Gleason 4+3=7 (grade group 3) and Stages T1–T2. For CPG 3, our clinician survey was unanimous in showing that physicians were not willing to place on active surveillance those men who had grade group 3 disease even if they were within CPG3. This is because evidence was quite clear that these men fare much worse after radical treatment even when it is applied at the time of diagnosis and therefore active surveillance recommendations internationally and eligibility criteria for active surveillance studies have never included patients with an overall grade attribution of 4+3. Further our physician survey and wide international consensus is that there are certain histological subtypes which increase the risk of progression and increase the risk of recurrence after treatment and these subtypes will also be excluded as there will otherwise be lack of physician buy-in if we allow such patients to be recruited. These include GG2 that harbours intraductal carcinoma or lymphovascular invasion (2019 International Society of Urological Pathology Consensus Conference on Prostate Cancer Grading).

Diagnostic pre-biopsy MRI (either bi-parametric or multi-parametric) is optional. We are allowing either multi-parametric or bi-parametric as the follow-up scans in active surveillance that we are proposing will all be bi-parametric given that the international PIRADS committee have recommended this approach for surveillance MRI scans given that the value of

continuing to inject gadolinium in serial MRIs is questionable. If the patient has not had a pre-diagnostic MRI, a 12-month MRI will be required.

(ii) Exclusion criteria

Patients on active surveillance for greater than 9 months prior to consent. Our PPI co-applicants and focus groups were quite keen that we include as many men in the study as possible and therefore widen our inclusion criteria to permit those who have been on active surveillance up to 9 months prior to consent but before they undergo their one-year MRI scan if it is required. This allows us to exclude those men who have already undergone their NICE recommended one-year MRI (where required) and potentially repeat biopsy, as to do so otherwise would impact on our sample size assumptions.

Any absolute contraindication to MRI. It is likely that men who have an absolute contraindication to MRI will not fulfil the inclusion criteria to have a pre-biopsy diagnostic level MRI of the prostate and therefore ongoing surveillance MRIs will not be possible in this group. Increasingly, this group is diminishing with newer forms of hip replacement that do not impact on MRI quality, MR-compatible pacemakers and the use of bi-parametric MRI without contrast injection with gadolinium.

Unable to give informed consent to the study. We have outlined our plans to ensure that as many men are given the opportunity to participate and therefore our recruitment strategy will involve translation of documentation into a number of languages as well as easy to read recruitment documents for vulnerable individuals including those who may lack capacity but whose carers and legal guardians could give consent on their behalf.

5. PROCEDURES AND MEASUREMENTS

Prostate Specific Antigen measurements

There are currently no validated metrics such as a PSA doubling time or PSA velocity that indicates cancer progression. However, the EAU recommends a PSA doubling time of 3 years to trigger ‘for cause’ MRI and biopsy. The leeway for tests and appointments for PSA is +/- 6 weeks.

Magnetic Resonance Imaging

MRI conduct: A study-specific MRI QA/QC Standard Operating procedure (SOP) will be drafted building on our experience in the PROMIS, PICTURE and 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 consensus [22]. Our lead radiology co-applicants alongside the NCITA imaging QA/QC process, will conduct a quality review of MRI scans of all centres prior to recruitment and optimise where necessary. However, since NICE recommended the use of MRI pre-biopsy, most centres have already gone through such a process within their local Cancer Alliance networks through a programme of work instigated by NHS England and the devolved nations that many in our group led on [3] alongside membership of PCUK’s Prostate MRI national expert group for standardisation of mpMRI conduct [22,29] [34]. Patient preparation for the MRI scans will follow up-to-date guidance at the time of study set-up; the current guidance is set out in the

following documents: PI-RADS v2.1 manual https://www.acr.org/-/media/ACR/Files/RADS/Pi-RADS/PIRADS-V2-1.pdf?la=en and Brizmohun et al [22]. See MRI Conduct SOP.

Quality control of MRI: CRUK's National Cancer Imaging Translational Accelerator 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 at least 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. The pilot phase 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.

Radiology expertise: We will include 30 centres with a range of patient volumes. NHS Cancer Alliances have been engaged in a standardisation programme since 2017 for prostate MRI conduct and reporting and our proposal will involve three additional training and standardisation meetings for reporting using the PRECISE v2.0 system with the third day being conducted near the end of the pilot. Reporters will also need to complete or be a Faculty member of either the free PCUK/RCR-approved online course (https://prostatecanceruk.org/for-health-professionals/online-learning/courses-and-modules/courses/all-courses/mpmri-before-biopsy) or other approved courses (British Society of Uro-radiology, European Society of Uro-radiology, American College of Radiology). Finally, a minimum 5% of MRI scans will be double reported to evaluate inter-observer variability.

MRI Reporting scheme: we will use the latest version of the PRECISE v2.0 scoring system. See MRI Reporting SOP. The leeway for tests and appointments for MRI is +/- 6 weeks.

Biopsy

Targeting and systematic biopsy protocol: We will follow standard care for centres in terms of type of analgesia/anaesthesia. Centres can use local anaesthetic, sedation or general anaesthetic; transperineal or transrectal route and visual-registration or image-fusion targeting. The exact anaesthesia type (local only, sedation, general anaesthetic) and biopsy type (transperineal vs transrectal, image fusion vs visual-registration) will be recorded. Number of systematic cores will be set out in a SOP and centres will declare which systematic biopsy protocol they are using. 4-6 cores per target and unlimited targets in total per patient [Hansen et al, 2020; Leyh-Bannurah et al, 2020; Kenigsberg et al, 2018]. Targeted biopsies will be carried out first, in order to minimise the impact of swelling on obtaining accurate sampling of targets. See Biopsy SOP.

The EAU recommends regular biopsy in standard care every 2-3 years. In the new pathway, we will recommend biopsy when there is a change on the MRI or if there is a consistent rise in PSA over 3 readings that is concerning for progression even if the MRI shows no change and other factors such as infection or prostatitis have been ruled out. If the rise in PSA represents a PSA doubling time of < 3 years, when using at least 3 readings, then further investigations are recommended.

Histology

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

Validated patient reported outcome measures

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

- All patients

Functional status, anxiety and health-related quality-of-life for all patients at baseline and annually: EPIC (Urinary, Erectile and Bowel domains), HADS (Hospital Anxiety and Depression Scale), and the EuroQol (EQ-5D-5L) will be used in the study as a generic measure of health-related quality-of-life which can be linked to public preferences [Janssen et al, 2013].

- Patients undergoing biopsy

Patients will be asked to self-report pain and discomfort (referred to as pain hereafter) immediately after and seven days after biopsy on a 4-point Likert-type scale as none, mild, moderate, or severe. Specific related complications such as fever, flu-like shivers, pain, haematuria, haematochezia, and haemoejaculate will be self-reported at 35 to 90 days after prostate biopsy as absent or present following biopsy on a purpose designed questionnaire.

For each symptom, patients will be asked to score the degree of “problem” as none, minor, moderate, or major. This will be used to derive a binary outcome for each symptom (present/moderate/severe problem vs. absent /minor problem).

- Patients undergoing an MRI

A questionnaire on MRI related side-effects will be given to all patients to be completed after the MRI but before the biopsy (if they have a biopsy)

5.1 Identification and recruitment of participants

Patients will initially be approached by their clinical team including urologists, oncologists and specialist nurses, who can send the patient information sheets as well as links to recruitment videos online for them to view. If they are interested in the study, the research team will contact them to answer any further questions they may have about the study and for those who are interested in participating we will facilitate remote electronic consent. All participants must be provided with a Patient Information Sheet (PIS) which may be provided electronically using the Sealed Envelope database platform that complies with HRA-MHRA guidance on e-consenting. Participants must also be able to discuss the trial with the investigator prior to consent being obtained. Where it is not possible to do this in person, it may be conducted via a telephone conversation (following approval by an ethics committee). Confidentiality must be maintained and the method must be secure. An audit trail is present to confirm that the person providing the electronic signature is the participant.
We will use remote electronic consenting which we used over the Covid pandemic era as well as printed consent forms for those men who prefer this approach best.

5.2 Screening and pre-randomisation evaluations

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

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

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

We will also collect information about what treatment options are available for patients who have progression of the prostate cancer and what treatment they chose through multidisciplinary team (MDT) outcomes in the clinical records and clinic letters or entries by clinicians in the health records. Most patients with localised prostate cancer will be able to choose from a number of options that straddle active surveillance, focal therapy, radical surgery or radiotherapy (with some men started on androgen deprivation therapy),

depending on cancer risk. Recent NHS guidance in 2019 was changed to allow for patients with intermediate and low risk cancer to take longer than the previous 31/62-day targets permitted so patients' decision about final treatment choice can sometimes take up to 3 months. This means we will be able to collect final treatment decisions for most of our participants with this information collated directly from health records; this information is unlikely to be available prior to database lock for many patients recruited and biopsied in the last 3 months of recruitment, so the eCRF will reflect this but given the size of the study is unlikely to have an impact on these findings.

Participants will be asked consent to collect long-term healthcare information from national records (i.e., Office for National Statistics, NHS Digital, Office for Health Improvement and Disparities, and/or other applicable NHS information systems, or national databases) and through a direct approach from the research team at any timepoint within 10 years of consent. We will ask patients to give permission to be contacted by a member of the central / local study research team within 15 years of signing their consent form, after the study has ended to complete a questionnaire about their health status (including details of any other tests and treatment they have had since the study) and quality of life. If the patient decides to take part a member of the study research team may send this request to the patient's home address.

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

Health Status

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

As prostate cancer is often a slow-growing disease which may not develop or progress for many years we will also ask patients to give consent for us to keep personal data stored or accessed for an additional 15 years on the NHSCR (National Health Service Care Register) so that data from national registries can be evaluated. For instance, long-term survival information to be flagged through national registries, for example NHS Digital (previously the Health and Social Care Information Centre); Office of National Statistics (ONS) in England/Wales; General Register Office in Scotland; Hospital Episode Statistics (HES) or Office for Health Improvement & Disparities.

5.3 Randomisation and Blinding

Patients will be allocated in a 1:1 ratio to either regular MRI scans or the current NICE defined standard. Randomisation will be blocked (random block size) and stratified by MRI visibility of lesion (3 categories [no visible lesion, diffuse changes, discrete visible lesion]), cancer Grade Group (GG1, GG2) and time since diagnosis. The study allocation will not be blinded to patients or physicians.

5.4 Visit Schedule

Standard Care (control) Arm
Standard Care (control) Arm

	Screening	Consent					
Visit	**Biopsy date**	**1**	**2**	**3**	**4**	**5**	**6**
Month	0	Up to 9 months from biopsy date	12 *	24 *	36 *	48 *	60 *
Informed consent		X					
Inclusion & exclusion criteria	X						
Demographics		X					
Targeted medical history	X[1]						
PSA blood tests (as defined in Standard Care SOP)**			X[2]	X[2]	X[2]	X[2]	X[2]
PSA Doubling time (every 6 months (3 readings)) (https://www.mskcc.org/nomograms/prostate/psa_doubling_time)			X	X	X	X	X
Digital Rectal Examination (as defined in Standard Care SOP) (when clinically indicated.			X*	X*	X*	X*	X*
Bi-parametric MRI and outcomes** (only when indicated based on DRE or PSA doubling time)			?[3] / Δ	?[3]	?[3]	?[3]	?[3]
Biopsy and results (only when indicated based on MRI change / DRE / PSA Doubling Time)			?[4]	?[4]	?[4]	?[4]	?[4]
Patient questionnaires		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
Further treatment for prostate cancer			?[6]	?[6]	?[6]	?[6]	?[6]
Further treatment for lower urinary tract symptoms			?[7]	?[7]	?[7]	?[7]	?[7]

**From biopsy date*
*** The leeway for tests and appointments for MRI / PSA is +/- 6 weeks.*
Δ An MRI at 12 months is only indicated if the patient did not have an MRI scan pre-diagnosis.
[1] Prostate MRI and prostate biopsy details, current use of 5-alpha reductase inhibitors (e.g., finasteride or dutasteride), use of testosterone supplementation or androgen suppression medication, family history of prostate cancer (defined as any immediate family relative (parent, sibling, child) diagnosed with prostate cancer at any time), ethnicity (using the UK Office for National Statistics groupings).
[2] PSA blood tests to be taken 3 monthly every year for patients in control arm, from biopsy date
[3] MRI only if clinically indicated as dictated by Standard Care SOP

[4] Biopsy may occur as clinically indicated. Outcomes can be taken from the electronic health record.
[5] The schedule of questionnaires is referenced in section 5 Validated patient reported outcome measures and also within the Patient Reported Outcomes and Experience Questionnaire.
[6] Patients who have treatment for their prostate cancer should be noted whether due to progression or for patient choice.
[7] Drug treatment or physical / operative interventions for lower urinary tract symptoms

Intervention Arm

	Screening & Consent	**Consent**					
Visit	**Biopsy date**	**1**	**2**	**3**	**4**	**5**	**6**
Month	0	Up to 9 months from biopsy date	12 *	24 *	36 *	48 *	60 *
Informed consent		X					
Inclusion & exclusion criteria	X						
Demographics		X					
Targeted medical history	X[1]						
PSA blood tests * / **			X[2]	X[2]	X[2]	X[2]	X[2]
PSA Doubling time (every year (using 3 readings)) *(https://www.mskcc.org/nomograms/prostate/psa_doubling_time)*			X	X	X	X	X
Bi-parametric surveillance MRI and outcomes [Δ] / **			X[3]	X[3]	X[3]	X[3]	X[3]
Biopsy and results (in some patients as clinically indicated as defined in Intervention Care SOP)			?[4]	?[4]	?[4]	?[4]	?[4]
Patient questionnaires		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
Further treatment for prostate cancer			?[6]	?[6]	?[6]	?[6]	?[6]
Further treatment for lower urinary tract symptoms			?[7]	?[7]	?[7]	?[7]	?[7]

**From biopsy date*
*** The leeway for tests and appointments for MRI is +/- 6 weeks.*
[Δ]From diagnostic MRI date (if patient has had one)
[1] Prostate MRI and prostate biopsy details, current use of 5-alpha reductase inhibitors (e.g., finasteride or dutasteride), use of testosterone supplementation or androgen suppression medication, family history of prostate cancer (defined as any immediate family relative (parent, sibling, child) diagnosed with prostate cancer at any time), ethnicity (using the UK Office for National Statistics groupings).

[2] PSA blood tests to be taken 6 monthly every year for patients in the intervention arm, from biopsy date
[3] MRI every 1-2 years depending on baseline classification. GG2 disease or visible lesion (score 4 or 5 at baseline) to undergo annual MRI. GG1 and invisible lesion to undergo 2 yearly MRI. Clinical need for contrast MRI to be noted and results collated if done in addition to bi-parametric MRI.
[4] Biopsy as clinically indicated as defined in the Intervention Care SOP. Outcomes can be taken from the electronic health record.
[5] *The schedule of questionnaires is referenced in section 5 Validated patient reported outcome measures and also within the Patient Reported Outcomes and Experience Questionnaire.*
[6] Patients who have treatment for their prostate cancer should be noted whether due to progression or for patient choice.
[7] Drug treatment or physical / operative interventions for lower urinary tract symptoms

5.5 Follow-up

Standard care arm:
These reflect standard care and there will be no additional follow-up visits required for the study. See Standard Care Active Surveillance SOP.

Intervention Arm:
MRI based active surveillance. Patients with a visible lesion (score 4 or 5) or Grade Group 2 cancer will have PSA 6 monthly and MRI annually. As per international PIRADS committee guidance the surveillance MRIs will be bi-parametric MRI scans which last approximately 15 minutes and exclude gadolinium contrast injection.
Patients with invisible lesion and Grade Group 1 will undergo PSA 6 monthly and MRI in years 1, 3 and 5. In all patients, a targeted biopsy will be carried out if the MRI PRECISE v2.0 score is >/=4. See Standard Care Active Surveillance SOP.

5.6 Laboratory Evaluations

(i) Haematology

Not applicable

(ii) Biochemistry

Prostate Specific Antigen (PSA) testing will be carried out as per local standards using standard methods and protocols by the GP or in hospital. These blood tests are part of routine care, and no additional blood is taken for the purpose of this study in any participant.

(iii) Urinalysis

Not applicable

(iv) Exploratory / Research samples

Not applicable

(v) Sample storage and analysis

Not applicable

(vi) Incidental findings

Incidental findings on MRI will be stated on the clinical report and the local clinical team will take appropriate action commensurate with the finding(s).

6. INTERVENTION

6.1 Permanent Discontinuation of Study Intervention and Withdrawal from Study

(i) 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.

(ii) Withdrawal from Study

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

- Participant decision
- Loss to follow-up

(iii) Procedures for Withdrawal from Study

Patients may decide to opt out at any time. This is entirely within their right to do so. Such cases will be reported to the Research Team Office so that no further data are entered onto the database, as specified in the patient information leaflet and appropriate Standard Operating procedure. Data captured before consent was withdrawn will be used in the study, but no further data, beyond this date will be collected or used in any analysis. Reason for withdrawal should be recorded in the eCRF and medical records, if given by the patient. Our sample size calculation assumes a 5% withdrawal rate but if this exceeds that number, we will continue to recruit patients until the target number for each randomisation is met. Patients opting out of the study for undergoing the intervention can agree for ongoing data collection as we would analyse on an intention to treat basis and knowledge of whether progression occurred subsequently and any other treatments that the patient had would be included in the analysis.

7. SAFETY REPORTING

The Common Terminology Criteria for Adverse Events (CTCAE v5.0) will be used to report adverse events. Please refer to for further details:

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

7.1 Adverse Event (AE)

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

7.2 Adverse Event recording

For the purposes of the study, AEs will be followed up according to local practice until the event has stabilised or resolved, or the Follow-up Visit, whichever is the sooner. All AEs and SAEs will be recorded throughout the study and all SAES, where in the opinion of the Chief Investigator, the event is 'related' and 'unexpected' should be reported to the sponsor and also be reported to the REC.

(i) Severity of Adverse Events

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

(ii) Causality of Adverse Events

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

7.3 Serious Adverse Events (SAE)

(i) Definition of SAE

An SAE is defined as any event that

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

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

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

7.4 Reporting of SAEs

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

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality within 24 hours.

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

List of Expected Adverse Events

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

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

(i) Related SAEs

Related: resulted from administration of any of the research procedures

(ii) Unexpected SAEs

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

(iii) Reporting of SAEs that are related and unexpected

All SAEs should be reported to the Wales REC 7 where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the *NRES SAE form for non-IMP studies*. The Chief Investigator must also notify the Sponsor of all SAEs where in the opinion of the Chief Investigator, the event is 'related' and 'unexpected'. Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details of sponsor for reporting SAEs are as follows:

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

Chief Investigator:
Professor Hashim U. Ahmed
Imperial College London, Hammersmith Hospital Campus
E-mail: atlas@imperial.ac.uk
Follow-up of patients who have experienced a related and unexpected SAE should continue until recovery is complete or the condition has stabilised. Reports for related and unexpected SAEs should be unblinded prior to submission if required by national requirements.

(iv) Annual reporting of Serious Adverse Events

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

7.5 Reporting urgent safety measures

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

8. STATISTICAL ANALYSES

8.1 Sample Size and power considerations

The sample size is based on the following assumptions (references 43-47, 60-64):

- 25% of the study population have progression by 5 years
- The NICE defined strategy detects 50% of these progressive cancers (12.5% of study population)
- Regular MRI will detect 75% of these progressive cancers (17.5% of study population)
- 5% loss to follow up at 5 years (most surveillance studies have shown <5% loss to follow-up)

1,200 participants (221 events) are required to have 90% power to detect a difference, between the two groups, in time to progression (defined as months from randomisation to first evidence of disease progression), using the log-rank test (two-sided alpha=0.05), considering 24 months of accrual and minimum 60 months of follow-up. 1,263 participants will be randomised to allow for 5% loss to follow-up.

8.2 Planned recruitment rate

We will monitor recruitment and safety regularly throughout the trial. There will be an independent Trial Steering Committee (TSC) and Data and Ethics Monitoring Committee (DMEC) (see section G). The first 12 months of recruitment will be an internal pilot with an emphasis on ability to recruit, with targets at this stage being 216 men recruited from 12 centres. The pilot will be defined as per HTA guidelines, using a traffic light system of red (stop the trial), yellow (remedial provisions), green (continue).

Proposed length of internal pilot phase: 12 months

Pilot Trial Targets	Red	Amber	Green
% Recruitment threshold	<60%	60 – 99.9%	≥100%
Total number of participants recruited	<130	130-215	≥216
Number of sites opened (accounting for gradual site opening)	<6	7-11	≥12

In summary, if at least 216 patients are recruited in the pilot, we would expect the TSC to recommend continuation of the trial (in line with the HTA guidance regarding green threshold). If the pilot recruits less than 130 patients (<60% pilot target), then this indicates a recommendation for stopping unless there is a very good reason for delay and a convincing solution can be employed. If the pilot recruits 130-215 (60-99%) then, in discussion with the TSC and HTA, measures to improve recruitment may be needed in the main trial. We shall use the % targets (100%, 60-99%, <60%) to inform study management setting site-specific targets, depending on the expected recruitment as declared by each of our pilot sites. We shall monitor site recruitment regularly as part of study management and if sites are under-performing or delayed in set-up, we shall consider opening other sites from a reserve list.

Our centre survey, discussion with NCRI Prostate Research Group and patient focus groups indicate strong support for this study. Of the 40 centres responding to our feasibility questionnaire (48 physicians), 35 were willing to be recruiting sites. Based on the questionnaire, we estimate 30 open sites in the main phase, with approximately 5-7 eligible

patients per month per centre. Therefore, in our 12-month internal pilot we estimate a recruitment rate of 25% of patients from the eligible pool which will be the average recruitment rate in the main phase.

8.3 Statistical Analysis

Interim analysis

We will monitor recruitment and safety and formally review 12 months recruitment into the internal pilot as per RAG table. The trial committees will issue stopping guidance based on ability to recruit as set out in the criteria detailed in this proposal. The Independent Data Monitoring Committee (IDMC) will feedback to the Trial Steering Committee (TSC), and the TSC will provide advice for the funder.

An interim analysis of PROMS using validated questionnaires, compared to baseline, to measure impact on urinary, erectile and bowel function (EPIC) as well as cancer-related anxiety (HADS), and overall health-related quality of life (EQ-5D-5L) will be conducted at 12 months. In addition, an interim analysis of the MODrum questionnaire will be conducted at 12 months.

Primary outcome analysis

The primary analysis will be on an intention-to-treat (ITT) basis. The primary analysis will use a multivariable Cox Proportional Hazards regression model, adjusted for the randomisation stratification factors. The estimated hazard ratio (HR) will be presented with 95% CI and significance (p value). Kaplan-Meier curves will also be reported together with the median progression free survival for each treatment group. If the proportional hazard assumptions are not met, other appropriate time to event analysis methods for the analysis of the primary outcome will be used, e.g., an accelerated failure time model. As a secondary analysis of the primary outcome, absolute between groups difference in proportions of patients progressing at 5 years will also be presented and a logistic regression model, adjusted by the stratification factors, will be used.

Secondary outcomes analysis

Analysis of secondary outcomes will use multivariable logistic or linear regression, depending on the type of outcome data. MRI & biopsy-related adverse events and proportion of patients agreeing to a biopsy when clinically recommended will be reported using summary statistics. PROMS data will be analysed using mixed linear models to account for the repeated measurements in time.

Compliance to allocated surveillance strategy will be monitored and reported by study arm. In particular, compliance to each component of the intervention (PSA, rectal examination, MRI, biopsy) will be reported by study arm. During the course of the trial, compliance to each component will be reported to the DMEC to ensure compliance to the protocol and, if necessary, evaluation of the need for remedial actions. Rates of MRI in both arms will be regularly monitored throughout the trial and these will be reported to the DMEC during the periodical DMEC meetings. A statistical analysis plan, outlining all the data analysis and hypothesis tests, will be written and agreed with the TSC and DMEC before any look at the data.

Inter-Observer Reliability

Coefficients of reliability will be derived to determine inter-observer reliability (overall agreement and weighted kappa at each individual score and by dichotomised score at the PRECISE MRI threshold denoting progression. Although the local radiologist will report all images from their centre, in order to assess inter-observer variability, all MRI assessments will be randomly re-allocated to one of a panel of radiologists in equal numbers for re-assessment. The radiologists will perform the re-assessments blind to the results of the first assessment and first examiner, but clinical data will be made available.

Measurement of costs and outcomes

The economic evaluation will estimate the long-term health outcomes and NHS costs of MRI-based active surveillance compared to the NICE defined strategy and ascertain if the MRI-based strategy represents good value for money to the NHS. Cost and health outcomes associated with the interventions will be collected over the trial period. These costs and outcomes will be extrapolated and modelled over a longer time horizon than captured by the trial (e.g., lifetime of the patient). This will involve developing a decision-analytic model to predict long-term quality-adjusted life expectancy and NHS costs given the observed differences in the trial's primary endpoint of cancer progression at biopsy and relevant secondary endpoints. A model is required because a trial that could capture differences in risk of metastases, health-related quality of life, and life expectancy would be unfeasibly long and large (e.g., in our 5-year cohort study in the UK of MRI-based surveillance, metastases developed in 8/672 [45]). We will take the NHS and Personal Social Services perspective, consistent with that used by the National Institute for Health and Care Excellence, and follow relevant methods guidance for cost-effectiveness analysis [53-55].

Resource use and cost data for the trial period will be collected through annual patient-reported questionnaires and eCRF questions and using the ModRUM tool (a generic, modular resource-use measure designed for collecting self-report resource utilisation data) [67]. These resource use data will be multiplied by appropriate unit costs obtained from the NHS Reference Costs databases, the British National Formulary, and other published literature. Health outcomes will be expressed in terms of the quality-adjusted life year (QALY), which captures the impact of treatment on both mortality and morbidity by 'weighting' each period of follow up time by the value corresponding to the quality of life (using the EQ-5D-5L) during that period. The EQ-5D-5L will be administered at baseline and annually during the trial period. The EQ-5D-5L 'profiles' generated for each patient, at each follow-up point, will be valued using a set of estimated preferences based on the UK population. These scores will be converted into QALYs using area under the curve analysis. A review of the literature will be conducted to establish whether it is possible to make links between the outcomes measured in the trial and longer term health-related quality of life.

We will develop the model structure and select inputs based on a review of the cost-effectiveness literature and feedback from the research team (both clinicians and PPI representatives). We will use the trial to inform the risk of progression, costs (using data on tests, investigations and procedures conducted during the trial, and patient reported healthcare use), and health-related quality of life (via EQ-5D-5L) by trial arm, and pre- and

post-progression. For model parameters which cannot be informed by the trial (e.g., probability of developing distant metastases), we will conduct a review of cost-effectiveness models, updating a recent review [56], and app raising and selecting data sources given clinical and patient feedback. Cost and QALY data will be synthesised to generate an incremental cost effectiveness ratio (ICER), which is defined as the ratio of the mean difference in costs to the mean difference in QALYs between the alternative intervention strategies (i.e., MRI-based active surveillance versus the NICE defined strategy). In order to characterise the uncertainty in the data, probabilistic sensitivity analyses will be conducted and uncertainty relating to modelled assumptions using scenario analyses.

To help inform NHS decision making regarding the choice of intervention strategy, consideration will also be given to the feasibility of implementing MRI-based active surveillance in light of any capacity constraints on the health system. There may be additional capacity constraints such as variation in availability of MRI scans across the country, allocating time and staff to MRI, and the interdependence of different components on MRI. Standard approaches to economic evaluation do not account for additional capacity constraints on care [68]. Therefore, consideration will be given to the implications of capacity constraints bringing in insights from other fields, such as operational research, so that the impacts of the options available on population health can be generated [69].

9. REGULATORY, ETHICAL AND LEGAL ISSUES

9.1 Declaration of Helsinki

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

9.2 Good Clinical Practice

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

9.3 Research Ethics Committee (REC) Approval

(i) Initial Approval

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

(ii) Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval as instructed by the Sponsor. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to 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.

Amendments will be reviewed and approved by the Trial Management Group. Amendments will be version controlled and updated study documents have an updated version number and date. Approved amendments will be circulated to all sites and any online trial registries materials will be updated.

(iii) Annual Progress Reports

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

(iv) End of Trial Notification

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

9.4 HRA approval

Health Research Authority (HRA) approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing.

The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

9.5 Other Required Approvals

Not applicable

9.6 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF/CRF and reviewed by the Chief Investigator and reported to the ICTU Head of QA 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.

9.7 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 the National Institute of Health Research – Health Technology Assessment. There is no payment for taking part in this study. The researchers won't receive any personal payment over and above normal salary, or any other benefits or incentives.

9.8 Trial Registration

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

9.9 Informed Consent

All subjects must sign and personally date the REC approved Informed Consent Form after having received detailed written and verbal information about the reason, nature and possible risks associated with the research study.

The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment 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 signed Subject Information Sheet/Informed Consent Form document. The original Informed Consent Form should be retained with the source documents.

9.10 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 Subject Information Sheet and Informed Consent. A copy of the letter should be filed in the subject's medical records.

9.11 Participant Confidentiality

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

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

King's College London to be sent patients' NHS number and name to perform linkage to the NHS Information Centre and the NHS Central Register or any applicable NHS information system, if subject has given permission for this in their consent.

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 your 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.

9.12 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.

9.13 End of Trial

Last patient Last Visit

9.14 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.

10. DATA MANAGEMENT

10.1 Source Data

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

10.2 Language

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

10.3 Database

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

10.4 Data Collection

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

10.5 Archiving

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

11. STUDY MANAGEMENT STRUCTURE

11.1 Trial Steering Committee

A Trial Steering Committee (TSC) will be convened including as a minimum an independent Chair, independent clinician, the Chief Investigator and Trial Manager. The role of the TSC

is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter (See CR014). A lay person will be included.

11.2 Trial Management Group

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

11.3 Data Monitoring Committee

The DMC will comprise two independent clinicians with experience in clinical trials and an independent statistician. 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 (See CR014).

11.4 Early Discontinuation of the Study

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

11.5 Risk Assessment

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

11.6 Monitoring

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

11.7 Quality Control and Quality Assurance

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

The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd Edition).

11.8 Peer review

This study has been peer reviewed by funder NIHR-HTA, within the ICTU-Surgery Trials Forum at Imperial College London and detailed review by the NCRI (UK) Prostate Research Group (7/2/2022).

11.9 Patient and Public Involvement

PPIE during study development

We have conducted two focus group meetings of 2 hours duration each with 6-7 patients who were on active surveillance around the UK through a summary sent to Prostate Cancer UK's patient network. This involved the lead applicant professor Ahmed summarising the literature in an accessible format for these patients in a webinar which was followed by a broad group discussion of the advantages and disadvantages of active surveillance and the problems that the focus group participants felt that were pertinent within active surveillance. The participants fed back their concerns about regular biopsies and harms that these can often cause and their enthusiastic support for a strategy such as regular MRIs that could mitigate against the use of either regular biopsies or inaccurate surveillance using PSA blood tests or finger examinations.

Our original design was one in which we would test regular MRI scans against regular biopsies in the same cohort of patients, but it was quite clear that there was no support for such a strategy and that there would be little to no buying from patients who participated in the focus group. Interestingly this was also supported by our clinicians survey the majority of him also stated that such a design would not be acceptable. As a result of this strong feedback, our study design changed from one that was more heavily reliant on routine biopsy to one that required biopsy only when a suspicious change occurred as the patients were strongly opposed to routine invasive biopsy. This meant our study would be much more impactful as it would demonstrate the usefulness of regular MRI scans as they would be conducted and used by clinicians to make decisions about patients, and we could therefore compare that strategy to standard normal care that occurs in the NHS. I will study therefore moved to one that would be much more impactful in that a comparative randomise study was strongly supported by the focus groups who fully understood that in order to change practice for the greater good an RCT would be the best approach to meet our objectives.

We asked participants in the focus group about the frequency of testing and were able to use both existing literature but also feedback from these focus groups. We designed our intervention arm on this basis. Remarkably, all stated a willingness to participate in an RCT as the study would offer a chance of having regular MRI that they would not normally have. Further, the groups also asked that we take a more proactive approach to giving health advice such as dietary and lifestyle changes within our information sheets, which we thought was an excellent idea. We will co-design this advice when the study starts with our co-applicant PPI researchers as well as the focus groups and bringing in Dr Ali's work on vulnerable groups as well. We believe this proactive approach to broad healthcare advice

could have significant subsequent impact beyond the specific question of prostate cancer active surveillance. Finally, we have also incorporated feedback from the panel about compliance and spoken to our co-applicants about this as well as the wider research team. We will design an active surveillance booklet either used in a paper format or electronically so that patients are empowered to know when and which tests to have within the study. Chronic diseases such as prostate cancer are best managed alongside patients taking a proactive approach, but they do require the tools to do so.

Ongoing involvement

Three PPI representatives will be co-applicants, 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 in the 5 languages used for recruitment. Findings will be presented at international conferences and 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.

Our physician survey shows the 35 NHS centres willing to participate cover most regions throughout the UK and include Scotland and Wales. The centres serve areas which have large groups of Black, Asian and Polish communities as well as socio-economically deprived areas with predominantly White populations. A PPI focus group will meet to review patient material and recruitment strategies before pilot start 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.

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. Dr Ali has links to carer and patient advocacy and support groups through her previous research, such as Mencap and the Foundation for People with Learning Disabilities, 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. Ray Monk will be involved in analysis as he has a particular interest in MRI within the pathway and has specifically raised the issue of different types of resolution of scanners and different manufacturers. He has asked that the statistical analysis plan includes a broad exploration of different types of scanners within the NHS to determine whether these might have an impact on the monitoring of prostate cancer within the study. We will incorporate

this feedback and involve Ray within the analysis so that we can cluster different MRI scanners according to whether they are 1.5 Tesla or 3.0 Tesla resolution and we will also explore scanners which are greater than five years old compared to those purchased in the last five years.

11.10 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. 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 because of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed.

Permission from the Trial Management Group 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 for up to 1 month before any presentations or publications are produced. Lay summary of the results for public and patient engagement Webinar or podcast or both to publicise the result to patients and public,

A Clinical Study Report summarising the study results will be prepared and 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 (www.nihr.ac.uk/documents/nihr-open-access-policy/12251).

During the period of funding, our datasets will be collected and completed in the manner described above. We anticipate opening access beyond the existing research group within 24-months after funding is complete. 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 patient 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 (www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253). 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 Ahmed and Fiorentino.

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13. REVISION HISTORY

Version	Date	Summary of changes
1.0	30/MAY/2023	First version
2.0	07/DEC/2023	Addition of funder acknowledgement and disclaimer statement
3.0	19/NOV/2024	- Minor changes were made to include reviews made by Imperial ICTU QA team and to include SAE Categorisation information in section 7 Safety Reporting on page 29. - Clarification was made regarding the PSA test timeline in accordance with PIS v2.0. - Clarification was made to study design as requested by QA. - Admininisative changes on page 3 to update the Sponsor representative. - Admininisative changes on page 4 to update the Study Statistician. - Addition of new study statitician to the Trial on page 4 - Administrative changes on page 2 of the protocol to include the studies ISRCTN and Clinicaltrials.gov registration number. - Update made to main study procedure on page 9 of the protocol to rectal exam making it non-compulsory. This was done due to aid site activations as current practice at sites do not have the capacity to offer digital rectal

		exams for the duration of the study and for all active surveillance patients. - Changes made to inclusion criteria to remove diagnostic bi parametric or multiparametric MRI on page 9. This was removed due to a contradiction in the original protocol. We state that patients who have not had an MRI before biopsy can still be included in the study but will require a 1 year MRI. This permits us to include as many patients as possible. For this reason, the mandatory pre-diagnositc MRI has been removed from the inclusion criteria - Trial summary on page 9 of the protocol was updated to reflect changes made to inclusion criteria and main study procedures.

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: Imperial Prostate 9 – ATLAS (Approaches To Long-Term Active Surveillance)

Protocol Number: Protocol number 22CX7971

Signed: _____

Name of Chief Investigator: Hashim Ahmed
Title: Professor

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

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

Study Title: Imperial Prostate 9 – ATLAS (Approaches To Long-Term Active Surveillance)

Protocol Number: Protocol number 22CX7971

Signed: _____

Name of Sponsor's Representative
Title
Sponsor name

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

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

Study Title: Imperial Prostate 9 – ATLAS (Approaches To Long-Term Active Surveillance)

Protocol Number: Protocol number 22CX7971

Signed: _____

Name of Statistician
Title
Organisation/Company

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: Imperial Prostate 9 – ATLAS (Approaches To Long-Term Active Surveillance)

Protocol Number: Protocol number 22CX7971

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____

APPENDICES

Appendices should be additional information to the protocol and can consist of:

- *Common Terminology Criteria for Adverse Events (NCI CTC).*
- *RECIST criteria.*
- *WHO / ECOG Performance status.*
- *PIS, Consent form, GP letter (although may be more practical to have them separate).*
- *Summary of dose modifications.*
- *Schedule of events table.*