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Approaches to long-term active surveillance of patients with prostate cancer (IP9 – ATLAS)

Submission date 24/01/2024	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 07/02/2024	**Overall study status** Ongoing	
Last Edited 02/08/2024	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-a-new-way-of-doing-active-surveillance-for-prostate-cancer-ip9-atlas

Background and study aims
The aim of this study for patients on active surveillance for prostate cancer is to demonstrate that the use of regular MRI scans is better able to detect cancer progression over 5 years compared to the current NICE-defined strategy.

Who can participate?
Patients aged 18 years or above with a diagnosis of localised prostate cancer in the 9 months before the screening visit and who have chosen active surveillance

What does the study involve?
Patients will be randomly allocated to either MRI scans or the current NICE-defined standard. Current (NICE-defined active surveillance): PSA test 3 monthly in year 1 and then 6 monthly with rectal exam annually. MRI will be carried out at 12 months (if not had one at diagnosis). A biopsy will be required if indicated due to changes in rectal exam or PSA.
Planned (regular MRI-based active surveillance): Patients with a visible lesion or medium-risk cancer will have PSA 6 monthly and MRI annually. All other patients will undergo PSA 6 monthly and MRI in years 1, 3 and 5.
For all patients, a targeted biopsy will be carried out if the MRI PRECISE score is >/=4.

What are the possible benefits and risks of participating?
Participants will continue on their standard care pathway with monitoring, so will not be at risk of progression not being detected. Those patients in the intervention group 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.

Where is the study run from?
Imperial College London (UK)

When is the study starting and how long is it expected to run for?
October 2023 to June 2032

Who is funding the study?
National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) (UK)

Who is the main contact?
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Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
328263

ClinicalTrials.gov number
NCT06280781

Secondary identifying numbers
CPMS 59385, IRAS 328263

Study information

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

Acronym
IP9 – ATLAS

Study objectives
To demonstrate that the use of regular MRI scans is better able to detect prostate cancer progression in men over 5 years compared to the current NICE-defined strategy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 14/12/2023, Wales Research Ethics Committee 3 (Health and Care Research Wales, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; +44 (0)2922 941107, +44 (0) 2922 940954, +44 (0)2922 940963; Wales.REC3@wales.nhs.uk), ref: 23/WA/0323

Study design
Randomized; Interventional; Design type: Process of Care, Imaging, Active Monitoring

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet

Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Prostate cancer

Interventions
Patients with prostate cancer who have chosen active surveillance to manage the disease will be informed of the study using the patient information sheet as well as speaking to their clinical and research team. If they wish to participate, written informed consent will be taken.

Soon after consent, patients will be informed of their allocation. This will either be standard care active surveillance or the new regular MRI-based active surveillance.

Standard care:
These reflect standard care and there will be no additional follow-up visits required for the study. PSA blood tests will be carried out (at hospital or GP) every 3-6 months. Clinical examination will be carried out every year. In patients where these indicate a clinical suspicion of progression, further tests to detect or rule out progression of cancer will be carried out such as an MRI and biopsy. Follow-up in the study will proceed for 5 years after randomisation. Patients will be asked to fill in questionnaires about their health at the beginning and every year for 5 years.

Intervention:
PSA blood tests will be carried out (at hospital or GP) every 3-6 months. An MRI scan will be done once a year for 5 years for all men with Grade Group 2 cancer or a visible tumour on MRI. An MRI scan will be done at 1 year, 3 years and 5 years for all men with Grade Group 1 cancer or non-visible tumour on MRI. In patients where PSA changes or MRI changes indicate clinical suspicion of progression, a biopsy will be carried out to detect or rule out progression.

Follow-up in the study will proceed for 5 years after randomisation. Patients will be asked to fill in questionnaires about their health at the beginning and every year for 5 years.

The researchers will give all men in the study a booklet detailing what their active surveillance programme is and a table for them to write down their test results as well as take notes. The PPI representatives have also asked that we give some advice on dietary and lifestyle changes that might be of benefit to patients on active surveillance.

Analysis of secondary outcomes will use multivariable logistic or linear regression, depending on the type of outcome data. MRI & biopsy-related adverse events and the 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 with the allocated surveillance strategy will be monitored and reported by study arm. Compliance with each component of the intervention (PSA, rectal examination, MRI, biopsy) will be reported by study arm. During the trial, compliance with each component will be reported to the DMEC to ensure compliance with 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 upon with the TSC and DMEC before any look at the data.

Intervention Type
Other

Phase
Not Specified

Primary outcome measure
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 as:
1. Biopsy: grade progression to Grade Group 3 or greater or detection on biopsy of intraductal cancer or lymphovascular invasion. Many clinicians would include patients on active surveillance with a cribriform pattern on Grade Group so this is not a factor for progression.
2. 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.

Secondary outcome measures
1. Cost-effectiveness of revising the prostate cancer active surveillance protocol to incorporate regular surveillance MRI at 5 years. 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., the 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. The researchers 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.
2. Proportion of patients requiring biopsy measured at 5 years. Biopsy will be recommended when there is a change on the MRI or if there is a consistent rise in PSA over three 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.
3. MRI and biopsy-related adverse events: patients will be asked to self-report pain and discomfort (referred to as pain hereafter) immediately after and 7 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 the 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).
4. Type of treatment for patients who progress and those who do not progress (prostatectomy, radiotherapy, brachytherapy, focal therapy) collected from health records at 5 years
5. Type of treatment for lower urinary symptoms for patients who progress and those who do not progress, collected from health records at 5 years
6. Use of systemic therapy and type in those who progress and those who do not progress, collected from health records at 5 years

7. Compliance measured as the proportion having each test (PSA, rectal exam, MRI) at each allocated timepoint and the proportion agreeing to a biopsy when clinically recommended at 5 years
8. Patient-reported outcome measures (PROMs) measured using validated questionnaires:
8.1. Urinary, erectile and bowel function measured using Expanded Prostate Cancer Index Composite (EPIC) annually from baseline to 5 years
8.2. Cancer-related anxiety measured using the Hospital Anxiety and Depression Scale (HADS) annually from baseline to 5 years
8.3. Overall health-related quality of life measured using EQ-5D-5L annually from baseline to 5 years
8.4. Patients undergoing biopsy will be asked to self-report pain and discomfort (referred to as pain hereafter) immediately after and 7 days after biopsy on a four-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).
8.5. Patients undergoing an MRI complete a questionnaire on MRI-related side effects after the MRI but before the biopsy (if they have a biopsy)
9. Inter-observer variability in reporting surveillance MRI scans in the MRI group measured at 5 years

Longer-term follow-up:
All patients will be consented for linkage to national databases. Clinical outcomes can be collected after the study end on the use of subsequent tests and treatments as well as adverse events and survival at 5 years

Method/data source
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. 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 alongside membership of PCUK's Prostate MRI national expert group for standardisation of mpMRI conduct. 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.

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. The 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. Targeted biopsies will be carried out first, in order to minimise the impact of swelling on obtaining

accurate sampling of targets. 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.

The histological report will evaluate the following aspects for each target and each location of systematic biopsies carried out according to the Royal College of Pathology (UK) guidance number of biopsies, number positive for cancer, core length in mm, cancer presence, maximum cancer core length in mm (where continuous and discontinuous numbers are given, for the purpose of analysis, the continuous number will be used), primary, secondary and highest Gleason grade, 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).

Overall study start date
01/10/2023

Completion date
30/06/2032

Eligibility

Key inclusion criteria
1. Age 18 years or above (no upper limit)
2. Patients with a prostate (either cis-male gender or trans-female gender with no prior androgen deprivation hormone use at all)
3. Diagnostic bi-parametric or multiparametric MRI
4. Diagnostic systematic biopsy +/- targeted biopsy
5. A histological diagnosis of localised prostate cancer of low or intermediate risk

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Male

Target number of participants
Planned Sample Size: 1263; UK Sample Size: 1263

Key exclusion criteria

1. On active surveillance for greater than 9 months prior to the screening date
2. Contraindication to MRI or gadolinium contrast
3. Previous hip replacement to both hips
4. Contraindication to performing a biopsy guided by a transrectal ultrasound probe

Date of first enrolment
01/07/2024

Date of final enrolment
30/06/2027

Locations

Countries of recruitment
England

United Kingdom

Wales

Study participating centre
Charing Cross Hospital
Fulham Palace Road
London
United Kingdom
W6 8RF

Study participating centre
Morriston Hospital
Heol Maes Eglwys
Cwmrhydyceirw
Swansea
United Kingdom
SA6 6NL

Study participating centre
Frimley Park Hospital
Portsmouth Road
Frimley
Camberley
United Kingdom
GU16 7UJ

Study participating centre
Royal Devon and Exeter Hospital
Royal Devon & Exeter Hospital
Barrack Road
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EX2 5DW

Study participating centre
Ysbyty Glan Clwyd
Glan Clwyd Hospital
Rhuddlan Road
Bodelwyddan
Rhyl
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LL18 5UJ

Study participating centre
Southampton
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
Southmead Hospital
Southmead Road
Westbury-on-trym
Bristol
United Kingdom
BS10 5NB

Study participating centre
Norfolk and Norwich University Hospital
Colney Lane
Colney
Norwich
United Kingdom
NR4 7UY

Study participating centre
Basingstoke and North Hampshire Hospital
Aldermaston Road
Basingstoke
United Kingdom
RG24 9NA

Study participating centre
Chelsea & Westminster Hospital
369 Fulham Road
London
United Kingdom
SW10 9NH

Study participating centre
Royal Surrey County Hospital
Egerton Road
Guildford
United Kingdom
GU2 7XX

Study participating centre
Queens Hospital
Queens Road
Croydon
United Kingdom
CR9 2PQ

Study participating centre
Northampton
Northampton General Hospital
Cliftonville
Northampton
United Kingdom
NN1 5BD

Study participating centre
Darent Valley Hospital
Darenth Wood Road

Dartford
United Kingdom
DA2 8DA

Study participating centre
Bradford Royal Infirmary
Duckworth Lane
Bradford
United Kingdom
BD9 6RJ

Study participating centre
Kings College Hospital
Mapother House
De Crespigny Park
Denmark Hill
London
United Kingdom
SE5 8AB

Study participating centre
Maidstone
Maidstone Hospital
Hermitage Lane
Maidstone
United Kingdom
ME16 9QQ

Study participating centre
Milton Keynes General Hospital
Milton Keynes Hospital
Standing Way
Eaglestone
Milton Keynes
United Kingdom
MK6 5LD

Study participating centre
Freeman Hospital
Freeman Hospital
Freeman Road

High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Kingston Hospital
Galsworthy Road
Kingston upon Thames
United Kingdom
KT2 7QB

Study participating centre
Lister Hospital
Lister Hospital
Coreys Mill Lane
Stevenage
United Kingdom
SG1 4AB

Study participating centre
Watford General Hospital
60 Vicarage Road
Watford
United Kingdom
WD18 0HB

Study participating centre
St Peters Hospital
Spital Road
Maldon
United Kingdom
CM9 6EG

Study participating centre
The Hillingdon Hospital
Pield Heath Road
Uxbridge
United Kingdom
UB8 3NN

Study participating centre
St Thomas' Hospital
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Sponsor information

Organisation
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Sponsor type
University/education

Website
http://www.imperial.ac.uk/

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: NIHR152027

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
30/06/2033

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request. The publication will be in line with ICMJE requirements and therefore explicitly state the researchers' 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. The researchers will post the data-sharing opportunity on their university websites. They 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 (https://www.nihr.ac.uk/documents/nihr-open-access-policy/12251). During the period of funding, the datasets will be collected and completed in the manner described above. The researchers anticipate opening up 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. 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.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 2.0	07/12/2023	03/07/2024	No	No