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A clinical trial using a pragmatic randomised design to test new interventions in prostate diseases

Submission date
15/05/2020

Recruitment status
No longer recruiting

Registration date
27/05/2020

Overall study status
Completed

Last Edited
15/08/2024

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The aim of this study is to find out more about what happens to men who are being investigated for possible prostate cancer and to test how effective new ways of diagnosing or treating prostate cancer are in comparison with what happens now. The researchers want to do this using a trial design called Trials WithIn Cohorts or TWICS for short.
Randomised controlled trials (RCTs) are the current gold-standard way of seeing if new treatments are better than what doctors currently use. In RCTs everyone who participates is randomly allocated to one of two groups. These groups are kept as similar as possible. One group receives the new treatment and the other, the standard of care or sometimes a placebo treatment. The outcomes of the two groups are compared to see if the new treatment is better. Although RCTs are on paper an excellent way to test new treatments they carry challenges which make completing them difficulty in today's world.
The design for this study is different to a traditional RCT and has two distinct aspects. First, a large group of men, called a cohort, is recruited. Patients within this cohort can be vastly different. Each patient is followed up over time on a regular basis. Second, patients eligible for new treatments or interventions are invited at random to consider undergoing them. Patients are fully advised as to what they are, what the risks and benefits are and can agree or disagree with having it. The outcomes of those not invited are compared to those who are invited.

Who can participate?
Men aged 18 years old and over who are referred by their GP to a Urologist as they are concerned that they may have prostate cancer. This may be because their prostate blood test level, the PSA, is high for example, or it may be because their prostate felt abnormal when it was examined.

What does the study involve?
Participants are given an information sheet about the study. After consideration and discussion with the doctor or the research team they can agree to take part and join the cohort or not. If they decide to take part then they will sign a consent form and they will be asked to fill in some questionnaires. The research team will also collect information about their health directly from

their health records. Over time, the research team will contact participants for regular updates about their health. Occasionally, they may be invited to consider a new test or treatment in the manner described above.
Participants might be approached in the near or distant future about a new test or treatment if they are eligible for it. They will be given more information about what this test or treatment is if they are invited to consider it. Each new test or treatment will have its own ethics committee approved informed consent form and participant information sheet. If participants are not randomly allocated to consider a new test or treatment, they will continue to have their usual standard care and the information collected about them in the study will form the standard care group. Participants will not need to do anything else if this is the case. If they decline an invitation for a new test or treatment they will continue to have theirusual standard care and the information collected in the study will still be collected.
As this is a new type of trial design for prostate cancer the researchers would like to gather information from participants and healthcare professionals alike, as to how they experience and perceive the design. They may invite participants to consider an interview about the process but they are not obligated to take part in this.

What are the possible benefits and risks of participating?
The potential risks and disadvantages of taking part if participants are not undergoing a new test or treatment are the same as for usual standard care. If participants are invited to consider and decide to accept a new test or treatment the potential risks and benefits will depend on what that might be. This will be fully explained to them including all potential advantages and disadvantages before they need to make any decision about whether or not to accept it.

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

When is the study starting and how long is it expected to run for?
June 2020 to August 2022

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT04400656

Integrated Research Application System (IRAS)
272985

Protocol serial number
19CX5601

Study information

Scientific Title
PROState Pathway Embedded Comparative Trial: the IP3-PROSPECT study

Acronym
IP3-PROSPECT

Study objectives
Trial aims
In the pilot phase of PROSPECT the researchers are interested in investigating the a) acceptability and feasibility of establishing the cohort of men, i.e. putting the questions of Point of Consent One to men being referred for investigation of prostate cancer, and b) observing the cohort over the study period and collecting data on the participants pertaining to their disease, their treatment and their health status.

A) Acceptability
Aim 1.1: To determine what proportion of men with a clinical suspicion for prostate cancer will participate in an cmRCT
Objective 1.1a: To evaluate the proportion of patients approached who agree to participate in the longitudinal cohort. This will be done by calculating the participation rates from men approached for an invitation to PROSPECT
Aim 1.2: To explore barriers and facilitators to implementation of a cmRCT in order to improve and inform patient and/or physician trial information, study processes, interventions, and recruitment and retention of patients. This will be carried out by qualitative assessments in the following areas
Objective 1.2a: To investigate by interview the patient experiences and perspectives on:
Trial participation
- The point at which men are approached by the research team to enter the cohort:
- Barriers and facilitators to consent to participate in the cohort
- Barriers and facilitators to consent to future random selection to undergo a new healthcare intervention
- Acceptability of monitoring of health status and the tools used to do this in the cohort
Objective 1.2b: To investigate by interview the experiences and perspectives of healthcare professionals (doctors, nurses and admin staff) on:
- Trial design and information to patients and healthcare professionals
- Feasibility of future random invitation of participants to interventions
- Tools used for measuring health status

B) Feasibility
Aim 2.1: To determine the feasibility of recruitment and logistical implementation of PROSPECT in different data collecting centres based in different institutions. This will be broken down into the following sub-questions:
Objective 2.1a: Evaluating how the patients are successfully identified and the option of how inclusion in the trial is presented to them
Objective 2.1b: Evaluate patient questionnaire response rates for pre-treatment quality of life
Objective 2.1c: Evaluate patient questionnaire response rates at pre-determined intervals following on from the point of recruitment into the trial to determine how to promote optimal patient response rate and improve data collection
Objective 2.1d: To evaluate completeness and fidelity of clinical data on the men who participate in the cohort

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval 29/05/2020, HRA London - Fulham Research Ethics Committee (HRA NRES Centre Manchester, Barlow House, 3rd Floor, 4 Minshull Street, M1 3DZ, UK; +44 (0)207 1048098; fulham.rec@hra.nhs.uk), REC ref: 20/LO/0459

Primary study design
Interventional

Study design
Cohort multiple randomised controlled trial (cmRCT) design (aka trials within cohorts [TWICS])

Study type(s)

Other

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

Interventions
PROSPECT is a cohort multiple RCT (cmRCT). The key features of a cmRCT are;
1. Explicitly-consented recruitment of a large cohort of patients with the condition of interest.
2. Regular measurement of relevant outcome measures for the whole cohort prospectively in the long-term.
3. Facility to re-approach cohort participants, who are randomly selected from eligible patients within the cohort, inviting them to undergo intervention of interest to researchers with eligible patients not randomly selected being part of the control standard care group.
4. “Patient-centred” informed consent. The consent process aims to replicate that used in the routine health care setting. Once the patient has been randomly selected from the eligible patients within the cohort, the second consent process should include detailed and specific information pertaining to the particular intervention or change in management they are being invited to undergo for comparison. Such information will be written and advised using patient representatives and undergo a new submission and review by the ethics committee.
5. Comparison of the outcomes in the randomly selected patients with the outcomes in eligible patients not randomly selected.
6. Capacity for multiple randomised controlled trials over time within the cohort simultaneously.

Consent
For men who are participating in the cmRCT there are two points of consent:

Point of consent 1 - assessed in pilot phase
At Point of Consent One men who are referred for investigation of prostate cancer will be asked two questions. The first questions relates to whether they are willing to join the cohort and have data collected directly from them over time on a regular basis. This data will include health-related quality-of-life data (at recruitment, 6 months, 12 months and yearly thereafter), linkage to their medical records so that researchers can know what happens to them over time, and access to other data about them held on national health registry databases. Also at point of consent, prospective participants will be asked (second question) whether they agree to being randomly selected in the future to interventions or changes in management in order to compare to standard care. The researchers will explain that this second invitation will be on a random basis. In other words, everyone eligible within the cohort will have the same chance of being randomly selected. The patient would still have the option of saying ‘no’ after the random selection when they are approached.

Participants:
Below is a schedule of visits for the study. In the pilot study, visits 0, 1, 2, 3, 4 and 5 will be carried out at a minimum but further follow-up in the study may not continue if further funding is not obtained. Patients will thusly return to standard of care follow-up in NHS practice.

Study visit schedule
Visit 0: Point of Consent 1 and screening:
Men who have been identified as eligible for the trial and received the Participant Information Sheet and interested in participating, will attend this screening and consent visit with their local

hospital research team. This will start with a consultation with one of the clinical research team. The patient will have the opportunity to raise any questions they have about the study and will sign the informed consent form if they are happy to take part.

Optional consent:
Standard of Care test results (Blood, Imaging, Biopsy)
As standard of care tests are performed as part of this study. The researchers would also like to know if patients are willing for us to store and use their data to see if new ways of looking at this data can detect cancer better in the future.

Health status
At the screening visit, patients will also be asked to give optional 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. The researchers 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 your name and NHS number 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 to see if anyone gets cancer in future and about the type of cancer and the treatment they have had. Results of your optional health status check will also help us in any future upcoming studies. Further ethical approvals with be sought and obtained for use of this data, if required.

Future contact
As prostate cancer is often a slow-growing disease which may not progress for many years the researchers will also ask patients if they are happy to keep personal data to be stored or accessed for 10 years on the NHSCR (National Health Service Care Register) after study end date.

In order to reduce the burden of visits the researchers will perform all these screening tests /consent and assessments in a single visit.

Visit 1 (0 Months):
A complete medical and urological history will be obtained at this visit. Demographic information obtained will include month and year of birth, age and ethnicity. Medical history will include all significant prior and current conditions, diseases and procedures not related to urology. Urological history will include all conditions and procedures related to urology. The World Health Organisation performance status will also be documented.

A baseline PSA level, measured from blood drawn by venepuncture, will be performed as it would be as standard NHS care.

At this visit each participant will be asked to complete four validated questionnaires. These are the EPIC bowel and bladder questionnaire (EPIC-26), The International Prostatic Symptoms Score (IPSS), the UCLA Prostate cancer index and the EuroQol (EQ-5D-5L). These can be completed in 1 of 3 ways. First. Each patient may be sent a link, via email, to the questionnaires which may be filled out remotely and on completion are directly uploaded to the study RedCap electronic case report form (eCRF). The participant's email address, along with their other personal identifiable data will be pseudonymised and housed separately to the eCRF which can be linked to via their unique trial identification number and stored on secure NHS computers. Second, the questionnaires may be directly inputted into the RedCap eCRF from a university tablet device from clinic. Third, sent out from the central PROSPECT team (Imperial College London) by post.

Visit 2 (0-6 months):
Collection of data at this time point will be permissible via postal, electronic, telephone or face-to-face communication. Unless the patient requests face-to-face visits they will only require attendance for hospitals visits that are defined by the local hospitals follow-up protocol within standard care.

Additionally the patients GP may be contacted for updates on the participant's medical or procedural history.

At this visit the patient will be asked to undergo the NHS standard of care diagnostic tests for prostate cancer. This will include a PSA blood test, an MRI scan of the prostate and if necessary (e.g., if a lesion is seen on the MRI scan) a transperineal prostate biopsy, As part of the preoperative assessment, a urine sample will be needed for culture. The radiological and histological results will be recorded as will the grade and stage of any cancer diagnosed.

A complete medical and urological history will be obtained at this visit. Demographic information obtained will include month and year of birth, age and ethnicity. Medical history will include all significant prior and current conditions, diseases and procedures not related to urology. Urological history will include all conditions and procedures related to urology.

Again, At this visit each participant will be asked to complete four validated questionnaires. These are the EPIC bowel and bladder questionnaire (EPIC-26), The International Prostatic Symptoms Score (IPSS), the UCLA Prostate cancer index and the EuroQol (EQ-5D-5L).

Visits 3 (6 months) and 6 monthly intervals thereafter to at least Visit 5 (24 months longitudinal follow-up). Collection of data at these time points will be permissible via postal, electronic, telephone or face-to-face communication. Unless the patient requests face-to-face visits they will only require attendance for hospitals visits that are defined by the local hospitals follow-up protocol within standard care.

A complete medical and urological history will be obtained at these visits. Demographic information obtained will include month and year of birth, age and ethnicity. Medical history will include all significant prior and current conditions, diseases and procedures not related to urology. Urological history will include all conditions and procedures related to urology. This will include any NHS standard of care treatment or investigation the patients has undergone for their disease such as prostatectomy, radiotherapy, CT and nuclear medicine bone scans.

Additionally the patients GP may be contacted for updates on the participant's medical or procedural history.

Again, at these visits each participant will be asked to complete four validated questionnaires. These are the EPIC bowel and bladder questionnaire (EPIC-26), The International Prostatic Symptoms Score (IPSS), the UCLA Prostate cancer index and the EuroQol (EQ-5D-5L).

Qualitative sub-study:
Here, the researchers intend to perform semi-structured interviews of at least 5 men who agree to join the study and those who do not. The interviews may be conducted in two way, either face-to-face or by telephone. Whilst the intention is to conduct at least 5 of each interview, the researchers will continue them until no further qualitative themes emerge from them.

At the first study visit as stipulated above, each participant will be asked to sign two separate informed consent forms (one for each interview type), giving their consent to be interviewed as to their thoughts of the study. As always, they may withdraw their consent for this at any time, and if they do not wish to give consent for this they can still continue in PROSPECT.

Healthcare professionals:
Semi-structured telephone interview aimed to elicit themes of views about PROSPECT and the cmRCT trial design will be conducted at 6 and 12 months following the opening of PROSPECT. The researchers aim to interview between 5 and 10 healthcare professionals.

Intervention Type
Other

Primary outcome(s)
1. Acceptability:
1.1. Rate of consent to inclusion to PROSPECT cohort at the original point of contact by the research team. This will be calculated on an ongoing basis and will be reviewed at 6 months and 1 year from opening and at the end of the study period
1.2. Experiences and perspectives of patients, by interviewing the patients who:
1.2.1. Consented to inclusion in the cohort study
1.2.2. Declined to enter into the cohort
1.2.3. Consented to inclusion in the cohort initially but who subsequently requested to leave the cohort
Structured thematic interviews will be conducted by the researchers who will follow the Interview Questionnaire Template. The interviews will be recorded and transcribed in house before analysis and theme-based extraction of the reasons behind men's decision regarding inclusion in the cohort. Recruitment for qualitative interviews will continue until no further themes emerge (time frame: 22 months)
1.3. The opinions of healthcare professionals who regularly look after men with prostate problems will be sought through semi-structured interviews that focus on implementation, practicality and efficiency of PROSPECT. There will be a different Interview Questionnaire Template for interviews with healthcare professionals (time frame: 6 months, 12 months)
2. Feasibility:
2.1. Evaluation of the number of men approached to enter PROSPECT against the number of men referred to the participating centres for investigation of prostate cancer (time frame: 22 months)
2.2. Review of the pathway by which PROSPECT approach men to invite them to the cohort. Part of this will be included in the qualitative interviews with men and healthcare professionals. Particular points of interest will be the timing of consent process, the trial personnel who gain consent, and the number of men who give consent who are subsequently not diagnosed with prostate cancer (time frame: 22 months)
2.3. Quality of life measured using EQ5D-5L at the point at which they consent to inclusion into PROSPECT. Data completeness will be calculated at 6 months after opening and on an ongoing basis as long as the study is open (time frame: 6 months, 12 months)
2.4. Disease-specific quality of life measured using questionnaires on disease-specific quality of life at the following points: recruitment to cohort, 0-6, 6, 12, 18, 24 months from recruitment to cohort, yearly questionnaires thereafter during inclusion in the cohort if trial remains open (i.e., post pilot phase)
PROSPECT will use three self-reporting quality of life validated questionnaires. The responses from the questionnaires will be of value as they will provide an informative vignette of the experience of men after the diagnosis of prostate cancer and they can be compared against the

experience of men who are investigated for but not diagnosed with prostate cancer. In terms of evaluating the feasibility of the cmRCT design, PROSPECT will calculate the rates of response from participants with these questionnaires. Questionnaire response rates will also inform PROSPECT of the understanding of the acceptability of the cmRCT design study to patients (time frame: 0-6, 6, 12, 18, 24 months from recruitment to cohort)
2.5. Feasibility of collecting data from the participating centres evidenced by the completeness of data for cohort participants including:
2.5.1. Subject data: age, co-morbidities, ECOG/WHO Performance Status, ethnic risk, family risk
2.5.2. Disease characteristics: PSA, MRI (volume, score), biopsy findings (cancer or not, grade if cancer, length of maximum cancer, other pathology), TNM stage if cancer
2.5.3. Treatment data: modality, follow-up, adjuvant and salvage treatments, mortality
Analysis will be conducted at 1 year after opening the PROSPECT and yearly thereafter in order to monitor any trends in improving or faltering data accrual on participants, as long as the study is open (time frame: 24 months after opening PROSPECT and yearly thereafter in order to monitor any trends)

Key secondary outcome(s)
1. The integrated qualitative component will explore patients who:
1.1. Consented to inclusion in the cohort study
1.2. Declined to enter into the cohort
1.3. Consented to inclusion in the cohort initially but who subsequently requested to leave the cohort
Structured thematic interviews will be conducted by the researchers who will follow the Interview Questionnaire Template. The interviews will be recorded and transcribed in house before analysis and theme-based extraction (time frame: 22 months)
2. The opinions of healthcare professionals who regularly look after men with prostate cancer will be sought through conducting semi-structured interviews that focus on ethics, implementation, practicality and efficiency of PROSPECT. There will be a different Interview Questionnaire Template for interviews with healthcare professionals (time frame: 6 months, 12 months)

Completion date
31/08/2022

Eligibility

Key inclusion criteria
1. Men aged 18 years old and over who are referred for investigations for urinary symptoms or elevated serum prostate specific antigen (PSA) levels or other risk factors for possible prostate malignancy
2. An understanding of the English language sufficient to understand written and verbal information about the trial and consent process
3. Estimated life expectancy of 5 years or more
4. Signed informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
Male

Key exclusion criteria
Men who are unable to give informed consent

Date of first enrolment
08/09/2020

Date of final enrolment
31/01/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Imperial College Healthcare NHS trust
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Fulham Palace Road
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Study participating centre
Ashford & St Peters Hospitals NHS Foundation Trust
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Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Research organisation

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Other unpublished results	version 1.0	20/09/2022	23/11/2023	No	No
Other unpublished results	version 1.0	10/03/2023	15/08/2024	No	No
Protocol file	version 6.0	05/04/2022	23/11/2023	No	No
Statistical Analysis Plan	version 1.0	11/04/2022	23/11/2023	No	No
	Study website				

Study website	11/11/2025	11/11/2025	No	Yes