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CHRONOS: Comparative health research outcomes of novel surgery in prostate cancer

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Registration date 28/11/2019	**Overall study status** Completed	
Last Edited 29/04/2025	**Condition category** Cancer	

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-comparing-the-outcomes-of-different-treatments-for-prostate-cancer-chronos-a#undefined (added 16/07/2020)

Background and study aims
Prostate cancer is the most common cancer in men in the UK. The prostate is a small gland in the pelvis, found only in men. About the size of a satsuma, it's located between the penis and the bladder, and surrounds the urethra. The main function of the prostate is to produce a thick white fluid that creates semen when mixed with the sperm produced by the testicles. The causes of prostate cancer are largely unknown. The chances of developing prostate cancer increase as you get older. Most cases develop in men aged 50 or older.
Men diagnosed with significant prostate cancer currently undergo radical therapy (RT) directed to the whole prostate (radiation used to kill cancer cells [radiotherapy] or surgery to remove the prostate [prostatectomy]). These provide good cancer control but can cause significant side effects.
Another type of treatment called Focal Therapy (FT) involves targeting only the cancer, whilst leaving healthy prostate gland alone. This has been shown in small scale studies to give similar successful treatment as RT but with fewer side effects.
However, there have been no randomised controlled trials (RCTs) comparing the success in cancer control and the quality of life in participants that undergo RT vs those that undergo FT. Further, there is a need to assess the use of additional therapies that may improve the cancer control outcomes following FT.
This trial is composed of two studies (A and B). CHRONOS-A will compare RT's to FT's, whilst CHRONOS-B will compare FT alone to FT with various drug treatments that can shrink the cancer before it is treated. We think this might improve outcomes for men that definitely want FT.

Who can participate?
Men (18 years +) with a diagnosis of medium/low risk prostate cancer proven on biopsy. Participants should be interested in undergoing FT as a treatment and be fit to undergo RT or FT, with no previous prostate cancer treatments.
The cancer must still be contained inside the prostate although if there is early involvement of the lining of the prostate, the participant may still be eligible.

What does the study involve?
The pilot study aims to see if men are willing to take part in the study, before a larger study with hundreds of men (the second stage) can be conducted comparing these treatments.
Participants will be able to choose whether they would like to participate in CHRONOS A or B.
We are also conducting an optional embedded study, assessing why participants choose to participate in trials like this. This will involve an extra visit for an interview with a member of the research team.

CHRONOS-A main study:
Participants will have an equal chance of being in the RT (Group 1) or FT (Group 2) based on random selection to ensure the treatments will be compared fairly.
Group 1 treatment: Radical therapy (radiotherapy or prostatectomy)
RT is either surgery or radiotherapy. The whole prostate is treated. Radiotherapy involves using x-rays to treat the prostate over several visits in hospital. Surgery involves open/keyhole removal of the prostate completely, under general anaesthetic. If the participant has been allocated to the RT group, they will decide which type of RT they will receive.
Group 2 treatment: Focal therapy (cryotherapy or High-Intensity Focused Ultrasound [HIFU])
These treatments do not target the whole prostate. HIFU involves an ultrasound probe that concentrates sound-waves to an area to heat it and cryotherapy involves needles inserted through the skin in front of the back passage that make ice-balls inside the prostate.

CHRONOS-B main study:
CHRONOS-B will compare the outcomes of those men who have FT (cryotherapy or HIFU) with those that undergo FT combined with additional testosterone lowering medication before the FT treatment.
All men will get FT in CHRONOS-B however they will be randomly placed into 1 of the 3 groups below, but will be able to decide whether they receive cryotherapy or HIFU as part of their FT treatment:
Group 1: FT alone.
Group 2: 12 weeks of finasteride followed by FT
Group 3: 12 weeks of bicalutamide followed by FT

What are the possible benefits and risks of participating?
There will be no direct benefit to the participant. The main benefit being the information we can gather to improve future treatment options for men with prostate cancer.

Radical Radiotherapy:
Advantages: Well known long term cancer control & survival outcomes; Requires no surgery /anaesthetic; Short treatment sessions
Disadvantages: Urinary leakage/ erectile dysfunction/bowel changes; Requires multiple hospital visits; May worsen urinary tract symptoms

Radical Prostatectomy:
Advantages: Well known long term cancer control & survival outcomes; Normally only requires 1 hospital visit
Disadvantages: Urinary leakage/ erectile dysfunction/bowel changes; Requires general anaesthetic; Risk of surgery (including damage to nearby structures and significant bleeding); Involves hospitalisation

Focal HIFU:
Advantages: Less side effects after treatment compared to radical therapy; Medium cancer

control & survival outcomes
Possible disadvantages: Requires general anaesthetic; Long term cancer control & survival outcome is not known; May require a repeat focal therapy/ whole gland treatment; Treatment may not be available at the local hospital so travel may be required

Focal Cryotherapy:
Advantages: Less side effects after treatment compared to radical therapy; Medium cancer control & survival outcomes; Can be performed under spinal anaesthetic
Disadvantages: Requires general anaesthetic; Long term cancer control & survival outcome is not currently known; May require a repeat focal therapy/ whole gland treatment in the future; Treatment may not be available at the local hospital so travel may be required

Advantages of additional bicalutamide or finasteride treatment: Testosterone is known to cause prostate cancer to grow. If we can block its action, we can shrink the prostate and cancer cells. Focal therapy might work better if we can shrink the cancer and prostate and reduce the amount of blood supply to their cancer cells beforehand with hormone treatment
Disadvantages of additional hormonal treatment: Most patients (>50%) will experience one or more of these side effectswith bicalutamide during the time the tablets are taken with some effect for 4-6 weeks afterward: tiredness, decreased sexual drive, weight gain, breast swelling and breast tenderness. Some patients with finasteride can experience side effects such as tiredness, decreased sexual drive during the time the tablets are taken.

Where is the study run from?
1. Imperial College NHS trust, UK - lead centre
2. Royal Marsden Hospital, UK
3. Guys and St Thomas' Hospital, UK
4. Whittington Hospital, UK
5. Kingston Hospital, UK
6. Wexham Park Hospital, UK
7. Sunderland Royal Hospital, UK
8. Southampton General Hospital, UK
9. Ashford & St Peters Hospital, UK
10. Hampshire NHS Foundation Trust, UK
11. Frimley Park Hospital, UK
12. Freeman Hospital, UK

When is the study starting and how long is it expected to run for?
The study started in March 2019 and is expected to run until December 2027

Who is funding the study?
Prostate Cancer UK

Who is the main contact?
Professor Hashim U Ahmed, Chief Investigator, hashim.ahmed@imperial.ac.uk
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Contact information

Type(s)
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Additional identifiers

Clinical Trials Information System (CTIS)
2019-001365-32

ClinicalTrials.gov (NCT)
NCT04049747

Protocol serial number
19CX5006

Study information

Scientific Title
Comparative Health Research Outcomes of NOvel Surgery in prostate cancer

Acronym
CHRONOS

Study objectives
The aims of the studies are as follows:
CHRONOS-A
Pilot: To determine if men will agree to participate in an RCT that randomly assigns them to focal therapy alone or radical therapy (radiotherapy or prostatectomy).
Main: To determine if focal therapy alone is non-inferior when compared to radical therapy (radiotherapy or surgery) in terms of progression-free survival (PFS) at 5 years in men with clinically significant non-metastatic cancer.

CHRONOS-B
Pilot: To determine if men expressing a preference for focal therapy will agree to participate in a multi-arm, multi-stage (MAMS) RCT that randomly assigns them to focal therapy alone or focal therapy in combination with neoadjuvant and/or adjuvant agents.
Main: To determine if focal therapy combined with neoadjuvant and/or adjuvant agents, compared to focal therapy alone, will improve failure-free survival (FFS) at 5 years, in men with clinically significant non-metastatic cancer

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/08/2019, HRA London - South East Research Ethics Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8068; NRESCommittee.London-SouthEast@nhs.net), ref: 19/LO/0712

Study design
Two parallel randomized controlled trials

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions
The pilot study uses the same methodology as the main study, however the primary objectives are to ascertain the feasibility of recruitment and retention of patients into both CHRONOS A and CHRONOS B. Data collection will be the same in the pilot as in the main phase (same eligibility criteria, same MRI requirements prior to focal therapy, same PSA and PROMS follow up, and all focal therapy patients will require MRI and biopsy at 12 months should they be in the trial at this point in the management).

The pilot will randomise over 12 months (but may finish early if recruitment targets are hit earlier). The patient visit schedule will be the same as in the main study, therefore they will be incorporated in the main study should recruitment be successful and funding secured. The main

study if it opens will continue for a further 5 years of recruitment. If the pilot is not successful in recruiting or funding not secured patients from the pilot will continue 3 months of follow up under the trial then continue management under local standard of care.

CHRONOS-A
Arm 1 (Control): Radical therapy (radiotherapy or prostatectomy [radiotherapy can be external beam or brachytherapy]). In patients undergoing radiotherapy a maximum of 6-months neo-adjuvant hormonal therapy will be allowed. In patients undergoing radical prostatectomy, cytoreduction of maximum 6 months with medication will be permissible, provided this is part of local practice.
Arm 2 (Intervention): Focal therapy alone (high intensity focused ultrasound [HIFU] or cryotherapy as per physician and centre choice). A second focal therapy session in-field, or a first focal therapy session to an out-of-field progressive or de novo lesion will be allowed as part of the focal therapy intervention.

CHRONOS-B
Arm 1 (Control): Focal therapy alone (high intensity focused ultrasound [HIFU] or cryotherapy as per physician and centre choice). A second treatment in-field, or a first focal ablation to an out-of-field progressive or de novo lesion will be allowed but will be regarded as failure events for the purpose of CHRONOS-B.
Arm 2 (Intervention): Neoadjuvant finasteride 5 mg once daily for a minimum of 12 weeks followed by focal therapy (as per control arm).
Arm 3 (Intervention): Neoadjuvant bicalutamide 50 mg once daily therapy for a minimum of 12 weeks followed by focal therapy (as per control arm).
Other arms can be added in future with protocol amendments.

Recruitment and randomisation of patients in the pilot and main study for CHRONOS will be the same, and if continuing to the main study, patients already recruited into the pilot will continue follow up and incorporated into the main study analysis.

Randomisation will performed using the latest update of –nstage- software, providing a 1:1 randomisation of patients in CHRONOS A and 1:1:1 randomisation of patients for CHRONOS B. Randomisation is based on the following strata:
- Tumour grade (Gleason 6 [grade group 1], Gleason 7 [grade group 2], Gleason 7 [grade group 3])
- Local stage (T2 versus radiological (MRI) T3)
- CHRONOS-A only: previous or current 5-alpha reductase inhibitor use

Intervention Type
Mixed

Primary outcome(s)
CHRONOS-A and CHRONOS-B Pilot
1. Feasibility of randomisation measured using number of patients recruited by 12 months
2. Acceptance of randomisation (rate per-month, per-centre) measured using number of patients recruited by 12 months
3. Compliance to allocated arm measured using number of patients undergoing intervention randomised to by 12 months

CHRONOS-A main trial:
1. Progression-Free survival (PFS) defined as biochemical failure (radical therapies only) or salvage therapy (local or systemic) or prostate cancer metastases or prostate cancer-specific mortality measured at 5 years

CHRONOS-B main trial:
1. Failure-Free survival (FFS) defined as more than one focal therapy session or salvage therapy (local or systemic) or prostate cancer metastases or prostate cancer specific mortality measured at 5 years

Key secondary outcome(s))

Pilot:
1. Patients' experience of consent and recruitment, including reasons for declining participation measured using qualitative interviews during the pilot trial period.
2. Patients' motivation to accept randomisation to, and compliance with, an intervention and understanding of each trial arm measured using qualitative interviews during the pilot trial period.
3. Patients' experience of each arm including systemic issues, erectile dysfunction, urinary symptoms and rectal symptoms measured using qualitative interviews during the pilot trial period. These will also be noted quantitatively using validated questionnaires at enrolment, 3- and 12-months post-treatment (International Index of Erectile Function-15, EPIC-26, EPIC Urinary domain, International Prostate Symptom Score and CTCAEv4.0 bowel domain).
4. Healthcare professionals' attitudes to intervention arms and trial design and whether this might impact on recruitment measured using qualitative interviews after consenting patients during the pilot phase.
5. Proportion of patients successfully recruited into each of CHRONOS-A and CHRONOS-B measured at 12 months
6. Potential improvements to recruitment processes measured using thematic analysis after review of audio-recording of the consent process and interviews from patients and clinicians during the pilot.
7. Feasibility of an economic evaluation alongside the main trial measured using EQ-5D-5L at the end of the pilot.

Main trial
1. Disease control:
1.1. Rates of positive biopsy for any prostate cancer and significant cancer defined by a number of different thresholds on biopsy following focal therapy (treated and untreated side) measured at 12 months and at any point in which a 'for cause' biopsy was performed during the 5 year follow up period
1.2. Rates of second or third focal therapy sessions, in-field or out-of-field measured during the 5 year follow up period
1.3. Rates of radiotherapy as adjuvant or salvage therapy following surgery or focal therapy measured during the 5 year follow up period
1.4. Rates of prostatectomy as adjuvant or salvage therapy following radiotherapy or focal therapy measured during the 5 year follow up period
1.5. Rates of systemic therapy as adjuvant or salvage therapy following surgery, radiotherapy or focal therapy measured during the 5 year follow up period
1.6. Rates of prostate cancer-specific mortality documented during 5 years of follow up
1.7. Rates of all-cause mortality documented during 5 years of follow up
1.8. Long-term health outcomes of those participants consenting to longitudinal follow-up will be reported in subsequent studies pending further funding measured at 10 years after signing their consent form
2. Adverse events and functional outcomes:
2.1. Rates of cystoscopic interventions following treatment measured at 5 years post-treatment
2.2. Rates of implant insertion for treatment of incontinence and erectile dysfunction measured at 5 years post-treatment

2.3. Rates of medication and/or pump devices used for erectile dysfunction following treatment measured at 5 years post-treatment
2.4. Rates of endoscopic investigations of the lower bowel following treatment measured documented during 5 years of follow up
2.5. Rates of pad-use and quantity per day for urinary incontinence following treatment measured documented during 5 years of follow up
2.6. Rates of pad-use and quantity per day for faecal incontinence following treatment measured at 5 years post-treatment
2.7. Rates of adverse event rates and complications measured at documented during 5 years of follow up
2.8. Genito-urinary and rectal side-effects using patient-reported measures at 3- months post-treatment, 12 months post-treatment and annually thereafter for a total of 5 years using: International Index of Erectile Function-15, EPIC-26, EPIC Urinary, International Prostate Symptom and CTCAEv4.0 bowel domain
3. Health economics:
3.1. The NHS costs of the different interventions measured using EQ-5D-5L at 3- months post-treatment, 12 months post-treatment and annually thereafter for a total of 5 years
3.2. The incremental cost per quality-adjusted life-year (QALYs) gained over the estimated lifetime of participants measured using information regarding health care resource uses over 5 years post-treatment
4. Qualitative:
4.1. Analysis of the impact on participants' overall health-related quality-of-life including adverse events and impact on genito-urinary and rectal functional status using questionnaires above conducted at the end of the study
4.2. Descriptive analyses of the questionnaire data, and use of questionnaire and qualitative interview datasets in a multi-methods analysis to look for overarching themes in barriers and facilitators to participation conducted at the end of the study
5. Imaging and Pathology: Accuracy and variability of multi-parametric MRI (mpMRI) in detecting disease at baseline
6. Translational, Biobank and Databank: Localisation and nature of cancer-infiltrating immune cells and the immune-relevant gene expression within the cancer tissue measured using matched blood, serum, plasma, pre-digital rectal examination urine, FFPE biopsy samples and imaging at 3, 12, 24, 26, 48 and 60 months post-treatment, where these samples have been provided and scans performed.

Completion date
20/03/2023

Eligibility

Key inclusion criteria
1. PSA </=20 ng/ml
2. Undergone a diagnostic pre-biopsy MRI compliant with national uro-radiology consensus guidelines. Dynamic contrast enhancement using gadolinium is not required at diagnostic stage. However, contrast enhancement MRI will be required in those men who undergo focal therapy prior to focal therapy as a baseline for comparison during follow-up. In the absence of a compliant MRI (for clinical or other reasons), a transperineal template mapping biopsy using a 5-10 mm sampling frame will be required
3. Histologically proven prostate adenocarcinoma
4. Overall Gleason score of 7 (either 3+4=7 or 4+3=7) of any length or Gleason 3+3=6 provided > /=6mm cancer core length in any one core. Patients with Gleason 4+4=8 in some cores but where

the overall Gleason score is 7 will be included.
5. Bilateral histologically proven prostate cancer is permissible provided the following criteria are met:
5.1. The index lesion to be treated if focal therapy is used meets the above histological criteria.
5.2. The patient may have a PIRADS or Likert score 3, 4, 5 mpMRI lesion on the same hemi-gland (either right/left or anterior/posterior) as the histological index lesion
5.3. Secondary areas of Gleason 3+3=6 of </=5mm cancer outside of the treatment field can be monitored, if present, and patient undergoes focal therapy.
5.4. If a Likert or PIRADS score 3,4 or 5 mpMRI lesion is present in an area outside of the treatment field with a negative biopsy for cancer then pathology must be reviewed and confirm the presence of inflammation or atrophy if the patient is to undergo focal therapy*
6. Radiological stage T2b/T3a will require central review regarding suitability for focal therapy.
7. Index tumour volume, as seen on mpMRI if carried out, will be restricted to 50% of one lobe for either unilateral or bilateral ablation, patients with tumour volume >/=50% of one lobe will require central review prior to enrolment. Final decisions on suitability of focal therapy will lie with the trial central review in these cases.**
8. No restriction exists in CHRONOS-A on previous or current use of 5-alpha reductase inhibitors or anti-androgens or LHRH agonists or LHRH antagonists.
9. Age at least 18 years of age
10. Participants must be fit to undergo all procedures listed in the protocol as judged by clinical team
*A biopsy of a suspicious mpMRI area may miss underlying cancer due to targeting error. However, if there is an alternative diagnosis for the changes on mpMRI such as inflammation or atrophy then this risk is reduced.
**This is to ensure that inappropriately large tumours are not being treated with focal therapy.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Male

Total final enrolment
100

Key exclusion criteria
1. Previous or current LHRH agonist or LHRH antagonist or anti-androgen use in CHRONOS-B.
2. Patients already established on a 5 alpha-reductase inhibitor (finasteride or dutasteride) who wish to go into CHRONOS-B will need to discontinue this for at least 6 months prior to randomisation. (NB: testosterone supplementation is permitted)

3. Previous treatment for prostate cancer
4. Life expectancy is likely to be less than 10 years
5. Unable to give informed consent

Date of first enrolment
30/11/2019

Date of final enrolment
12/11/2021

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Imperial College Healthcare NHS Trust
St. Marys Hospital
Praed Street
London
United Kingdom
W6 8RF

Study participating centre
University Hospital Southampton NHS Foundation Trust
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Southampton
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SO16 6YD

Study participating centre
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Aldermaston Road
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RG24 9NA

Study participating centre

Ashford And St Peter's Hospitals NHS Foundation Trust
St Peters Hospital
Guildford Road
Chertsey
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KT16 0PZ

Study participating centre
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United Kingdom
SL2 4HL

Study participating centre
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SR4 7TP

Study participating centre
Royal Marsden Hospital
Fulham Road
London
United Kingdom
SW3 6JJ

Study participating centre
Frimley Park Hospital
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Frimley
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GU16 7UJ

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Guys and St Thomas' Hospital
Great Maze Pond
London
United Kingdom
SE1 9RT

Study participating centre
Freeman Hospital
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Newcastle
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NE7 7DN

Study participating centre
Whittington Hospital
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N19 5NF

Study participating centre
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Kingston Upon Thames
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KT2 7QB

Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Charity

Funder Name
Prostate Cancer UK

Alternative Name(s)
Prostate Cancer, Prostate Action, ProstateUK, prostatecanceruk

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit 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	27/01/2023	29/04/2025	No	No
Participant information sheet	version v4.0	08/10/2019	05/12/2019	No	Yes
Participant information sheet	version v4.0	08/10/2019	05/12/2019	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version v3.0	08/10/2019	05/12/2019	No	No
Statistical Analysis Plan	version 1.0	10/03/2021	29/04/2025	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes