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Title: Comparative Healthcare Research Outcomes of Novel Surgery in prostate cancer

Authors: Deepika Reddy^{a,b}, Taimur T Shah^{a,b}, Tim Dudderidge^c, Stuart McCracken^{d,e}, Manit Arya^{b,f}, Chris Dobbs^g, Mark Emberton^f, Francesca Fiorentino^h, Emily Day^h, Toby Prevost^h, John Staffurthⁱ, Matthew Sydes^j, Mathias Winkler^{a,b}, Hashim U Ahmed^{a,b}

Affiliations:

- a) Imperial Prostate, Division of Surgery, Department of Surgery and Cancer, Imperial College London, London, UK
- b) Imperial Urology, Charing Cross Hospital, Imperial College Healthcare NHS Trust, London UK
- c) Department of Urology, University Hospital Southampton NHS Trust, Southampton, UK.
- d) Department of Urology, Sunderland Royal Hospital, Sunderland, UK.
- e) Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
- f) Department of Surgery and Interventional Sciences, University College London, and University College Hospital London
- g) Patient and Public Representative
- h) Imperial Clinical Trials Unit, Imperial College London, London, England.
- i) School of Medicine, Cardiff University, Cardiff, UK.
- j) Medical Research Council Clinical Trials Unit at University College London, London, UK

Corresponding author:

Deepika Reddy

Address: Imperial Prostate, Room 5L28, 5th Floor, Laboratory Block, Charing Cross Hospital Campus, Imperial College London, Fulham Palace Road, W6 8RF, UK

Email: Deepika.reddy06@imperial.ac.uk

Telephone: +447876763356

Abstract

Introduction: Focal therapy (FT) targets individual areas of cancer within the prostate, to confer oncological control with minimal side-effects. Early evidence demonstrates encouraging short-medium-term outcomes. With no randomised controlled trials (RCT) comparing FT to radical therapies, Comparative Healthcare Research Outcomes of Novel Surgery in prostate cancer (CHRONOS) will compare the cancer control of these two treatment strategies.

Patients and Methods: CHRONOS is a parallel phase II RCT for patients with clinically significant non-metastatic prostate cancer. CHRONOS-A will randomise patients to either radical treatment or FT. CHRONOS-B is a multi-arm, multistage RCT comparing focal therapy alone to FT with neoadjuvant agents that might improve the current focal therapy outcomes. An internal pilot will determine the feasibility of randomisation and compliance to allocation, whilst the proposed definitive study will recruit and randomise 1190 patients into CHRONOS-A and 1260 patients into CHRONOS-B.

Results: Primary outcome in CHRONOS-A is progression-free survival (the transition to salvage local or systemic therapy, development of metastases or prostate-cancer-related mortality) and in CHRONOS-B is failure-free survival (includes the above definition and recurrence of clinically significant prostate cancer after initial FT). Secondary outcomes include adverse events, health economics and continence, erectile and bowel function measured using validated questionnaires. CHRONOS is powered to assess non-inferiority of FT compared to radical therapy in CHRONOS-A, and superiority of neoadjuvant agents with FT in CHRONOS-B.

Discussion: CHRONOS will assess the oncological outcomes after FT compared to radical therapy and determine whether neoadjuvant treatments might improve cancer control following one FT session.

Keywords: Focal therapy, High-intensity focused ultrasound, cryotherapy, multi-centre, prospective study, prostate cancer

Introduction

Prostate cancer is diagnosed in 47,000 patients every year in the UK and about 192,000 in the USA (1, 2). Randomised controlled trials (RCTs) such as SPCG-4, PROTECT and PIVOT have shown that only patients with intermediate and high risk localised prostate cancer benefit from improved metastases-free survival at 10-15 years if they undergo radical therapy compared to active monitoring or watchful waiting strategies (3-5). However, radical therapies can lead to detriments in adverse events, genitourinary and rectal function. Incontinence after radical therapy has been reported as high as 20% and impotence rates reported between 30-60%. Further radical radiotherapy is associated with rectal morbidity, including bleeding, discomfort and stool changes in 5-20%. As many of these men treated with curative intent have a good life-expectancy, such morbidity can impact upon quality of life. Whilst there is an increasing recognition that low risk men should undergo active surveillance, there is a group of men with low volume intermediate or high cancers that might undergo tissue preservation strategy called focal therapy.

Background

Tissue preserving strategies are commonly used in many solid organs, including renal, breast and lung cancer (6-8). Precise cancer localisation is common theme amongst these, and it is only recently that within prostate cancer diagnosis has the use of MRI and targeted biopsy allowed this concept to now be entertained in prostate cancer (9). Focal therapy aims to preserve benign prostate tissue and reduce collateral damage to adjacent structures such as neurovascular bundles, external urethral sphincter, bladder neck, urethra and rectum that can occur with radical treatments (10).

Oncological outcomes show cancer-specific survival of >99% at a median of 5 years following focal therapy (11). A large systematic review demonstrated 15% of patients required a redo focal therapy treatment within 10 years due to either residual or recurrent disease (12). Other medium-term case series have shown further focal treatment can be required in 20-30% of patients and 5-10% require radical or systemic therapy over a median 5-6 years follow-up (11). Strategies that may reduce the need for further treatments following the initial focal therapy session might reduce patient and healthcare burden.

To date there has been no successful RCT comparing focal therapy to radical therapy. The Prostate Cancer RCT Consensus Group reviewed the cause of unsuccessful RCTs in this disease space, showing that physician and patient equipoise and failure to retain patients in the randomised arm as

predominant factors in eleven previous failed RCTs that compared different types of interventions for localised prostate cancer (13). A recent pilot RCT called Partial Ablation compared to Radical Therapy (PART- ISRCTN99760303) comparing focal HIFU to radical prostatectomy had a feasibility objective to meet a recruitment rate of 50% of men approached. However, after screening 356, 244 were eligible, of whom only 70 men accepted randomisation. 20% of those randomised to prostatectomy refused their allocation, but none declined in the focal therapy arm (14).

Mechanism of focal therapy failure

Failure of initial treatment may be due to progression of untreated low risk lesions, concomitant undiagnosed significant cancer, an inadequate ablative margin leaving satellite lesions untreated or sub-optimal ablative effect due to heat-sink effects countering thermal effects (figure 1). This all assumes that the operator is conducting the procedure to a high standard following appropriate training. CHRONOS requires all focal therapy surgeons to be vetted by a central board, to ensure appropriate experience.

Such mechanisms of failure are often targeted using neoadjuvant strategies in other solid organ tumours such as breast cancer, in which radiotherapy and/or tamoxifen is used after wide-local excision to improve cancer control(15). Further androgen deprivation therapy is commonly used to enhance clinical response to radical radiotherapy for prostate cancer (16).

The Four Reasons for Focal Therapy Recurrence

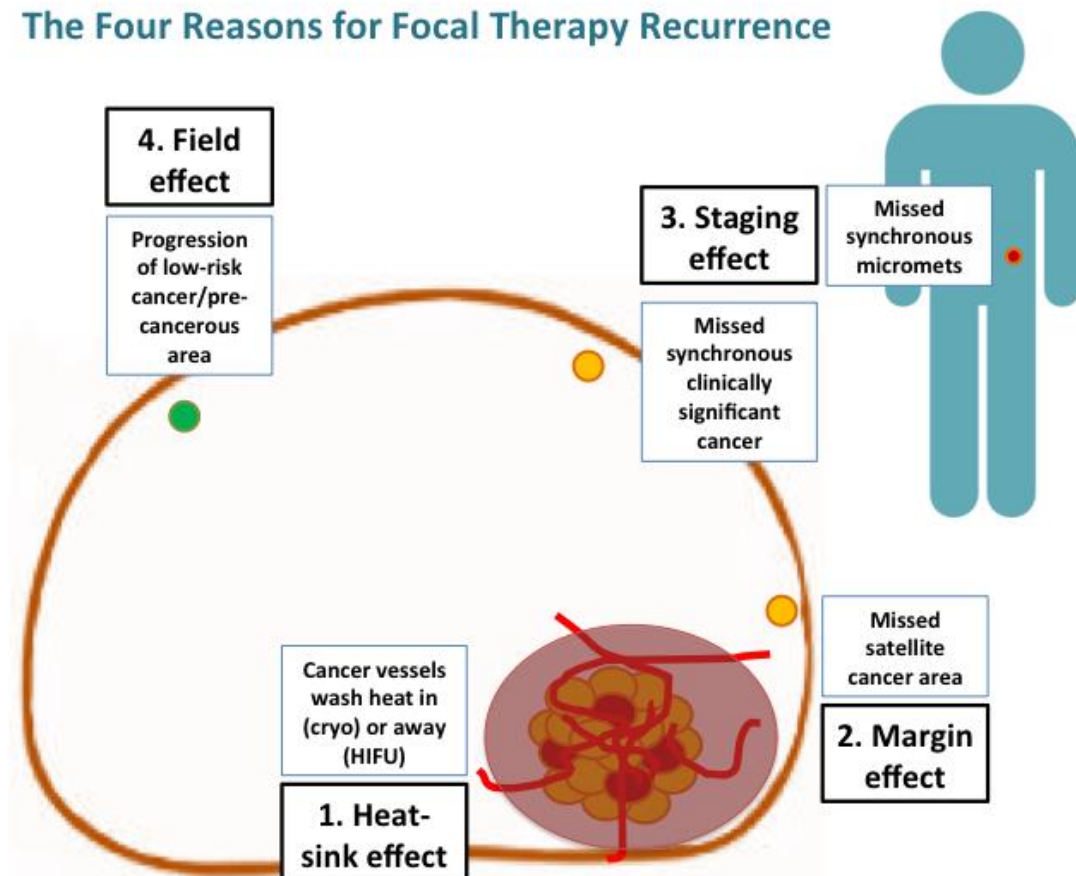


Figure 1: Causes of focal therapy recurrence/ failure

Use of neoadjuvant treatment

No high-level evidence has been published reporting the use of neoadjuvant treatment in the context of focal therapy for prostate cancer. Up to 20% of patients undergoing focal therapy are known to require re-treatment (11). We hypothesize that use of neoadjuvant agents will lead to improved local control after FT by a) improving cell kill at the surgical margins of ablation, b) improve cell kill at the centre of the tumour by reducing the heat sink effect, c) potentially reduce rate of secondary lesions progressing or developing and d) reduce any potential for micro-metastatic related late distant failure. We plan to consider various neoadjuvant strategies in CHRONOS-B that make mechanistic sense in potentially working alongside focal therapy, to reduce re-treatment rates.

Hormonal therapy (such as 5-alpha-reductase inhibitors, LHRH agonists, anti-androgen drugs or other novel hormonal agents) cytoreduces cancers, reduce/eliminate small low-grade tumours and decreases vascularity thus minimising the heat-sink effect that counteracts ablation (17, 18). Further, ablation has been shown to induce immunotherapeutic effects, therefore future neoadjuvant or adjuvant strategies might involve vaccines or other immune-modulating agents, resulting in

potentiated immune response and impact on residual tumours in-field, as well as potentially impacting on satellite lesions and out-of-field progression/de novo disease (19, 20). Metabolic agents such as metformin and low-dose cyclophosphamide are other possibilities.

Trial Information

Protocol Summary

CHRONOS is a prospective, multi-centre therapeutic phase II randomised controlled trial, conforming to Stage 2b/3 of the IDEAL clinical trial guidelines for evaluation of a surgical intervention. It is sponsored by Imperial College London, and the pilot is funded by the Prostate Cancer UK charity. The trial protocol was designed by investigators with input from patient representatives and patient focus groups. Monitoring of subject safety and study compliance is being managed by Data Monitoring and Trial Steering Committees.

Trial design

We will conduct a head-to-head RCT comparing focal therapy alone to radical radiotherapy/prostatectomy/ brachytherapy in CHRONOS A. As most centres do not offer focal therapy, we will test what levels of equipoise exist in those UK centres that do or don't offer FT.

Considering focal therapy is already offered in numerous centres in the UK under NICE Interventional Procedure (IP) guidance, some men and their physicians might have a strong preference for FT and therefore there is the opportunity for them to be recruited into CHRONOS-B, designed as a multi-arm multi-stage RCT, allowing all participants to undergo focal therapy.

Our proposal for a feasibility study in CHRONOS B aims to initially test two commonly used hormonal agents alongside focal therapy. CHRONOS B will randomise equally into a focal therapy alone arm, focal therapy with 12 weeks of neoadjuvant finasteride, or focal therapy with 12 weeks of neoadjuvant bicalutamide. Additional arms can be tested in future (e.g., immunotherapeutic agents, checkpoint-inhibitors, low-dose cyclophosphamide and other hormone treatments [abiraterone, enzalutamide, apalutamide]).

With such an array of agents and strategies that could be used, carrying out individual head-to-head RCTs would be inefficient and not cost-effective. The MAMS RCT design allows concurrent recruitment to multiple arms with early stop-points for ineffective interventions or those conferring too high an adverse event rate. Importantly, the MAMS trial design allows arms to be added over time, as and when both novel agents and funding become available, without having to start a new trial altogether (21). Use of existing processes further increases the efficiency of this trial design, enabling seamless

recruitment to research questions of interest, and reducing competing trials. With time, the control arm can also be updated with evidence-based proven therapies. Examples of such trial designs are seen in STAMPEDE, evaluating the use of adjuvant treatments in men with advanced prostate cancer, and EHVA T01 evaluating various HIV vaccines in the management of HIV- positive patients (22, 23).

CHRONOS is similar, albeit not equivalent, to the strategy used in PACE-A and PACE-B which tests the use of stereotactic radiotherapy against standard care in localised prostate cancer (ClinicalTrials.gov:NCT01584258). The benefit of our approach is that all patients would be offered both studies with those in equipoise participating in CHRONOS-A and those expressing a preference, participating in CHRONOS-B (figure 2). Provided patients meet the eligibility criteria for both trials, the decision of which trial to enrol into will depend upon clinician and patient discussion. Thus, the loss of eligible patients would be minimal and would likely maintain a high recruitment rate overall. Inability to recruit and retain patients within their randomised arm observed with traditional trial designs have led to the early termination or failure of previous attempts of head to head comparisons of focal therapy to whole gland treatments (13). We are initially conducting an internal pilot/feasibility study to assess patient acceptance of the design and compliance. A full sample size calculation for both the pilot and for the main stages has been provided, so that if funding were available, we would seamlessly run into the main stage of the CHRONOS.

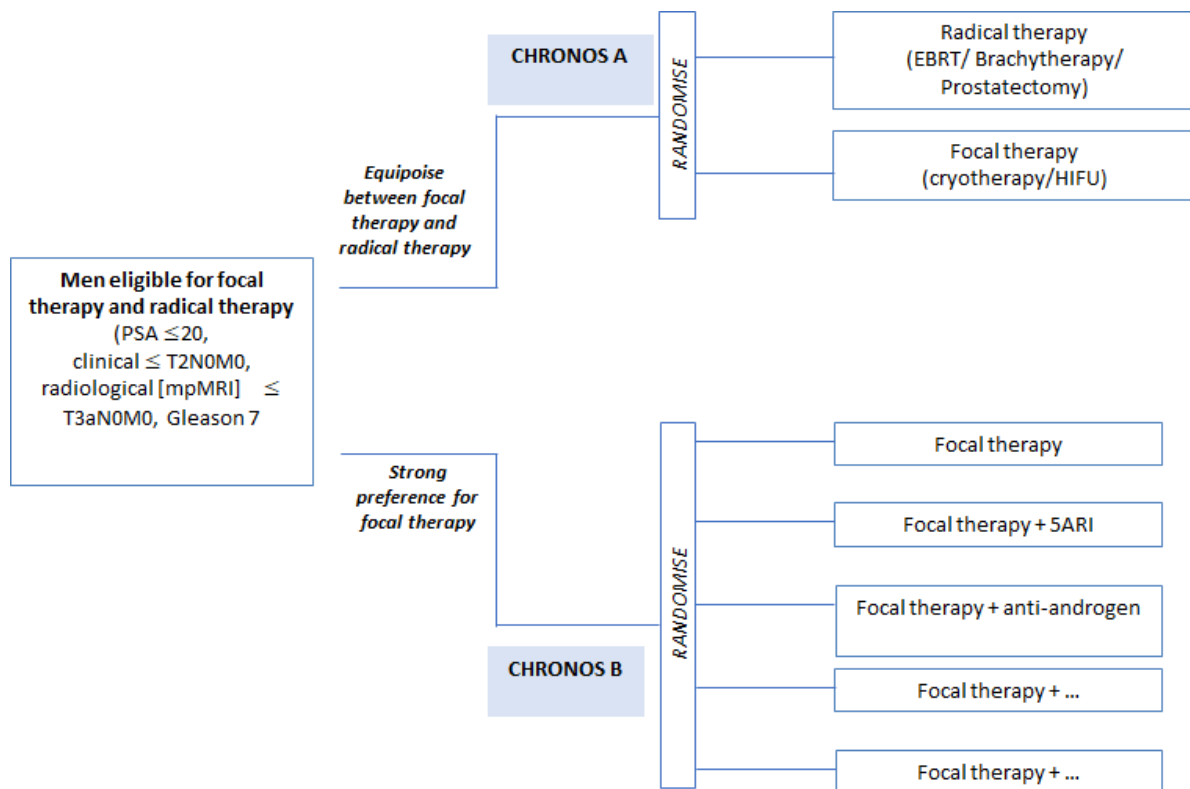


Figure 2: CHRONOS trial design

Study Objectives

The CHRONOS pilot will primarily evaluate the feasibility of recruitment of patients, and compliance to their allocated arm. If successful, the main study will evaluate progression-free survival in CHRONOS-A, and initial focal treatment failure-free survival in CHRONOS-B.

Secondary outcomes include:

- 1) determining the adverse events and functional outcomes after radical therapy, focal therapy or focal therapy with neo/adjuvant treatments,
- 2) to establish the NHS costs of the different interventions,
- 3) to determine the Cost per QALY, cost per PFS/FFS and costs and consequences,
- 4) to determine acceptability and completeness of resource use and utility measures (EQ-5D-5L)
- 5) patient experience of consent and recruitment, including reasons for declining participation,
- 6) Participants' motivation to accept randomisation to and compliance with an intervention, which may or may not include neoadjuvant and adjuvant treatments.
- 7) Patients' understanding and experience of each trial arm.
- 8) Patients' experience of toxicities, focusing on erectile dysfunction and urinary symptoms.
- 9) Patients' attitudes to the predicted survival rate.
- 10) Potential improvements to recruitment processes.

- 11) Healthcare professionals' attitudes to intervention arms and trial design and whether this might impact on recruitment.
- 12) To compare MRI outcomes with histology at time-points in which both are mandated.
- 13) To evaluate cancer infiltrating immune cells and immune gene signatures following ablation.
- 14) To build a biobank and databank of matched imaging, blood, serum, plasma and pre-digital rectal examination urine as well as FFPE biopsy samples.

Eligibility Criteria

The population choice was decided upon after reviewing multiple consensus groups, recommending disease and patient demographics indicative of patients with clinically significant prostate cancer that is unlikely to be metastatic at point of diagnosis as well as existing and past study eligibility criteria(24).

Patients will be screened for enrolment if diagnosed with histologically proven intermediate risk prostate adenocarcinoma (PSA \leq 20ng/ml, Gleason \leq 7, cT2N0M0/ rT3aN0M0) on any form of prostate biopsy. Decision for staging criteria is to represent diagnostic pathways of the recruiting sites. Consensus groups have determined the need to identify patients with clinically significant prostate cancer, whilst being amenable to focal therapy techniques (24). Patients must be at least 18 years of age, treatment naïve, and fit to undergo all procedures listed within the trial they propose to enrol into. Patients must have MRI findings concordant to biopsy result, and in those who are unable to undergo MRI must undergo transperineal template mapping biopsy using a 5-10mm sampling grid. CHRONOS-B has further exclusion criteria in which patients established on a 5 alpha-reductase inhibitor (finasteride or dutasteride) will need to discontinue this for at least 6 months prior to randomisation. No patient may enrol into CHRONOS-B if they have previously used or currently use LHRH agonist or LHRH antagonist or anti-androgen therapy. Patients will be recruited from UK based sites within the pilot and may include international sites within the main study.

Trial Entry

Eligible men will be identified via local site multi-disciplinary meetings and offered a patient information sheet in clinic. They will be invited to attend a screening and enrolment visit, in which the inclusion/exclusion criteria will be evaluated, treatment options will be discussed, and informed consent obtained. Patients will be enrolled and randomised within the same visit, in which validated questionnaires will be completed (EQ-5D-5L, International Index of Erectile Function-15, EPIC-26, EPIC Urinary domain, International Prostate Symptom Score and CTCAEv4.0 bowel domain).

Patients will also be asked to consent to optional biobanking of urine, blood and tissue taken during biopsy and/or prostatectomy. A further optional study is a qualitative research study, in which patients that enrol and decline enrolment into CHRONOS will be interviewed by a research group from Marie Curie Research Centre, Cardiff University. Those that enrol into the study will be invited to further interviews during the study period, evaluating the experiences within the trial.

Trial treatments

Patients randomised to the control arm of CHRONOS-A will have a discussion with their treating physician regarding which treatment choice of radical prostatectomy, radical brachytherapy or radical radiotherapy is recommended, and which is preferable to the patient. This should reflect current local practice. Focal therapy available within CHRONOS is HIFU or cryotherapy and determined by physician and patient choice and technical factors. Determination of focal therapy modality may depend upon one or a combination of location of disease, size of gland, presence of prostatic calcifications. Such disease characteristics may improve the success of one modality over another. Within CHRONOS-B pilot, patients randomised to the intervention arms will undergo focal therapy after 12 weeks of neoadjuvant therapy, either finasteride 5mg OD or bicalutamide 50mg OD. As with the multi-arm multi-stage trial design, arms may conclude or start according to trial results or according to current research and clinical results.

Radical Radiotherapy: CHRONOS has received RTTQA approval, and radiotherapy regimes will be reviewed by the Radiotherapy Quality Assurance Team. Treatment should mirror local clinical practice; however, the central trial centre recommends the use of 60Gy/27F with no lymph node treatment, unless approved by central review panel.

Radical Brachytherapy: Radical brachytherapy should be provided only in centres with enough experience to perform this procedure independently. Such treatment plans and procedures should reflect the treatment centres' local practice. Such centres will be screened by the RTTQA Quality Assurance Team, along with the treatment plans and post plans for patients enrolled into CHRONOS.

Radical Prostatectomy: The modality of radical prostatectomy (open, laparoscopic, robot-assisted laparoscopic) may be chosen according to clinical recommendation and patient choice. Clinicians are required to provide a quality assurance declaration, in order to ensure minimum outcome standards

are met within CHRONOS. Extended lymph node dissection is not permissible unless approved by the central review panel.

Focal therapy: In order to standardise treatment, the lead centre will provide information regarding how to deliver focal therapy, including acceptable treatment maps. Clinicians providing focal therapy are expected to have adequate experience to perform this procedure independently, and only approved clinicians may deliver focal therapy within CHRONOS. Local sites are encouraged to discuss and/or refer complex cases to the lead centre. CHRONOS does not mandate which machine/ technology is used.

Trial Mandated interventions: Patients randomised to focal therapy will require an mpMRI prior to focal treatment, and at 12 months post randomisation. The DCE sequence will be used to compare pre-treatment appearances to post-treatment. Patients undergoing radical therapy will not require this sequence, if not part of local practice. Further focal therapy patients will require a biopsy (performed by any route, and any methodology according to local practice) targeting the treated area at 12 months. In the absence of an mpMRI in focal therapy patients, a transperineal template mapping biopsy (5-10mm sampling density) is mandated.

Determination of failure events

In CHRONOS-A, Progression-Free Survival (PFS) is defined as biochemical failure (radical therapies only), salvage therapy (local or systemic) or prostate cancer metastases or prostate cancer specific mortality. After radical radiotherapy, a PSA rise of ≥ 2 ng/ml over the PSA nadir (Phoenix criteria), and after radical prostatectomy a PSA rise > 0.2 ng/ml will count as biochemical failure. Salvage local therapy following focal therapy will be defined as surgery or radiotherapy or 3 or more focal therapy sessions. Any radiotherapy given after prostatectomy will be counted as a failure event. In CHRONOS-B, Failure-Free survival (FFS) is defined as transition to one further focal therapy session or salvage therapy (local radiotherapy or surgery, or systemic) or prostate cancer metastases or prostate cancer specific mortality.

Follow up visits

Follow-up within the trial will reflect usual practice within the NHS. All patients will be reviewed 3 months after treatment, in which a clinical consultation will occur with PSA test, and PROMS questionnaires. Further follow up visits may be in person, or remotely. PSA tests are required at 12 months post randomisation, and every 6 months thereafter, PROMS are required annually and may

be completed in person or sent to local site teams via post or email. Focal therapy patients must, if not contraindicated, undergo an mpMRI with biopsy targeting the treated area, and any new areas of suspicion if noted upon mpMRI. If the patient is unable to undergo mpMRI, a transperineal template mapping biopsy is mandated.

For-cause tests

Follow-up imaging will not be protocol led, except after focal therapy at the 12-month post focal therapy time-point, but we recommend imaging to take place when there is suspicion of progression such as patients with a rising PSA (biochemical failure). The appropriate imaging will be chosen as per the local hospital resources and policies. We envisage that the majority will perform a combination of a prostate MRI, nuclear medicine bone scan, PET-CT/MRI, whole-body MRI or CT chest/abdomen/pelvis. In radiotherapy patients where there is suspected PSA relapse but the international definition of biochemical failure (PSA nadir plus 2.0ng/ml) has not been reached, evaluation should include a for-cause mpMRI and biopsy if required. As there is no defined time-point for a PSA nadir value following focal therapy the PSA value at 12-months post randomisation in patients with a negative mpMRI and negative control biopsy for clinically significant cancer will be used. Following this if there are any two further consecutive rises in PSA at least 3 months apart, with no influencing factors at the time (e.g., urinary tract infection, inflammation, instrumentation/procedures, biopsies, catheterisation), a for-cause mpMRI with or without biopsies can be carried out at the discretion of the treating clinician.

Health economics

A cost and consequences framework will be developed, in order to establish the NHS costs, to determine the cost per QALY and cost per progression/ failure free survival event. We will collect data on the costs of investigations, and management of adverse events experienced within each intervention. Further health-related quality of life due to adverse events within the trial will be reviewed using the EQ-5D-5L tool. In using such methods, the cost-effectiveness of the use of focal therapy will be directly compared to that of radical treatment options.

Statistics/ sample size calculation

- CHRONOS-A is designed to prove non-inferiority of focal therapy compared to radical therapy. In the main trial period, we aim to recruit 1190 patients over a total recruitment and follow-up period of 8 years.

- CHRONOS-B is currently designed as a three- arm MAMs RCT in which 1260 patients will be recruited over a total recruitment and follow-up period of 8 years.

The recruitment targets for both CHRONOS A and B will require an average of 1-2 patients recruited per centre per month. At a conservative rate, we expect to recruit 60 patients in the pilot stage in 10 centres in less than 12 months.

Sample size calculations below are for the full phase II studies based on progression-free survival (PFS):

CHRONOS-A: Progression-free survival (PFS) in our population at 5-years is approximately 85-90% after radiotherapy and similar for prostatectomy. Overall survival is high and being a 10-15 year outcome it will not be used in this study. PFS is a clinically meaningful endpoint, with precedence in other studies and can be measured in the same way in both arms (time to salvage therapies). Our hypothesis is that FT is non-inferior in terms of PFS, whilst having fewer side-effects. In the PART RCT pilot (prostatectomy versus FT), a failure of 25% (PFS 75%) for surgery compared to a maximum 35% after focal (PFS 65%) was accepted by the NIHR-HTA as a non-inferior design because the functional detriment would be substantially better. Our trial team believe it is reasonable to assume 85% PFS after radiotherapy with a non-inferiority margin of 5% for FT would meet clinical and patient acceptance.

Based on an allocation ratio of 1:1 and a non-inferiority margin of 0.05 with a 0.85 PFS rate in the standard care arm (at median 5-years), power 0.80 and alpha 0.05, drop-out after randomisation of 5%, the overall required sample size is 1190 with 136 expected total number of events. Total recruitment and follow-up period will be 8 years. If recruitment rates were deemed to be high then the power could be adjusted to 0.90 and the total sample size will be 1660 with 189 expected total number of events. This will be on the advisement of the TSC. PFS for the main Stage will be defined as transition to salvage therapies or metastases or mortality related to prostate cancer.

CHRONOS-B main stages II and III: Using the latest update of –nstage-, with an allocation ratio of 1:1:1, we anticipate approximately 1200 patients are required over 5 years to observe 120 control arm failure-free survival (FFS) events within 7.6 years. This time will be dependent on observed FFS event rates and assumes of 20 patients recruited per month. This calculation gives 85% power at the

efficacy stage analysis, to detect a hazard ratio (HR) of 0.67 and is based on 20% of patients having a FFS event by 3 years (30% by 5-years).

Long term follow-up

CHRONOS will aim to establish a better understanding of long-term health status and healthcare resource usage and quality of life after the main stage of the trial is completed. This is an optional component and patients who consent to providing identifiable data will be linked with the national databases (ONS and HES database. We will use such linkage to observe if anyone gets cancer in future and about the type of cancer and the treatment they have had.

We will also ask patients whether or not they give permission to be contacted by a member of the study research team within 10 years of signing their consent form, after the study has ended to assess their willingness 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 research team will check the hospital/GP records to ensure patient status before sending this request to the patient's home address.

As prostate cancer is often a slow-growing disease which may not progress for many years we will also ask patients if they are happy to keep personal data be stored or accessed for an additional 10 years on the NHSCR (National Health Service Care Register). This is an optional part of consent.

Discussion

CHRONOS is the first RCT comparing focal therapy to radical therapy or focal therapy with neoadjuvant treatment in patients with intermediate-high risk prostate cancer. The parallel RCTs allow recruitment into a trial that encompasses physician and patient equipoise and should optimise retention of patients into their randomised arms as well as offer a cost-efficient design that maximises involvement into trials. CHRONOS will also evaluate the health economic implications upon implementing focal therapy with or without neoadjuvant treatment.

Study limitations

The CHRONOS protocol may have some limitations. First, the lack of widely accepted PSA-based criteria to define failure after focal therapy may potentially bias in favour of focal when investigating and diagnosing recurrence or residual disease. An attempt of ameliorating this is to mandate a biopsy

of the treated area at 12 months post randomisation. However, as standard of care after radical therapy does not mandate imaging or biopsy, we recognise there is an element of imbalance between the radical and focal arms of CHRONOS-A. This type of issue is inherent in localised prostate cancer trials in which the intermediate endpoints by definition as using metastases or mortality would require expensive, unfeasible and logistically challenging large trials spanning 15-20 years which even if successful will be outdated by the time they do report (25, 26). For instance, PROTECT were criticised for using active monitoring which was not as rigorous as modern active surveillance(27). Second, the protocol allows for any form of biopsy, provided a mpMRI has been performed. This could allow for sub-optimal staging and grade diagnosis, although does reflect usual clinical practice and has better external validity.

Conclusions

The CHRONOS study will assess the oncological outcomes after focal therapy compared to radical therapy and determine whether neoadjuvant treatments might improve cancer control following one focal therapy session.

Trial status

Ethics committee approval has been granted by South London Research Ethics Committee (REC reference 19/LO/0712) and the trial is registered with clinicaltrials.gov identifier NCT04049747.

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Conflicts of Interest and other funding

Ahmed's research is supported by core funding from the United Kingdom's National Institute of Health Research (NIHR) Imperial Biomedical Research Centre. Ahmed currently receives funding from the Wellcome Trust, Medical Research Council (UK), Cancer Research UK, Prostate Cancer UK, The Urology Foundation, BMA Foundation, Imperial Health Charity, NIHR Imperial BRC, Sonacare Inc., Trod Medical and Sphiris Biocorp for trials in prostate cancer. Ahmed is a paid medical consultant for Sphiris Biocorp and Sonacare Inc. Ahmed, is a proctor for cryotherapy and paid for training other surgeons in these procedures. Ahmed is paid proctor for Rezum for the treatment of benign prostate hyperplasia. Winkler receives a travel grant and a loan of device from Zicom Biobot.

Mark Emberton's research is supported by core funding from the United Kingdom's National Institute of Health Research (NIHR) UCLH/UCL Biomedical Research Centre. He was awarded NIHR

Senior Investigator in 2015. Emberton receives funding from NIHR-i4i, MRC (UK), Cancer Research UK, Sonacare Inc., Trod Medical, Cancer Vaccine Institute and Sophiris Biocorp for trials in prostate cancer. Emberton is a medical consultant to Sonacare Inc., Sophiris Biocorp, Steba Biotech, Exact Imaging and Profound Medical. Emberton is a proctor for Irreversible Electroporation (Nanoknife) and is paid for training other surgeons in this procedure. Emberton has loan notes/stock options in Nuada Medical Ltd (UK).

Ahmed and Emberton are proctors for HIFU and are paid for training other surgeons in this procedure.

Shah receives funding from Prostate Cancer UK and the St Peters Trust for clinical research and has received funding for conference attendance from Astellas, Ferring and Galil Medical.

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