CLINICAL STUDY PROTOCOL

Full Study Title:

Comparative **H**ealth **R**esearch **O**utcomes of **NO**vel **S**urgery in prostate cancer

Short Study title / Acronym:

IP 4 – CHRONOS

Product: CHRONOS-A:
Radical therapy or focal therapy
Products: None

CHRONOS-B:
Focal Therapy or Neo/adjuvant medication plus Focal Therapy
Products: Neoadjuvant bicalutamide; Neoadjuvant Finasteride

Development Phase: Phase II/III

Sponsor: Imperial College London

Version no: 5.0

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This protocol has regard for the HRA guidance

Research Reference numbers

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CONTACT LIST

Chief Investigator

Name: Professor Hashim U Ahmed
Address: Room 5L28, 5th Floor, Laboratory Block, Charing Cross Hospital Campus, Imperial College London, Fulham Palace Road, London W6 8RF
Tel: 0203 311 1673
Fax: N/A
Email: hashim.ahmed@imperial.ac.uk

Sponsor

Sponsor's Name: Imperial College London
Address: Joint Research Compliance Office (JRCO), Room 215, Level 2, Medical School Building, St Mary's Campus, Norfolk Place, London W2 1PG

Name of contact person: Ruth Nicholson
Title: Head of Research Governance and Integrity Team
Tel: 0207 594 9459
Email: r.nicholson@imperial.ac.uk

Funder

Funder's name: Prostate Cancer UK
Address: 53 Tooley St, London SE1 2QN

Clinical queries should be directed to the ICTU Study Manager who will direct the query to the appropriate person:

ICTU Study Manager

Name: Dr Thiagarajah Sasikaran
Address: Imperial College London
Division of Surgery, Charing Cross Hospital, 5L15, Laboratory Block, Fulham Palace Road, London, W6 8RP
Tel: 0207 594 6017
Email: t.sasikaran@imperial.ac.uk

ICTU Operations Manager

Name: Mrs Natalia Klimowska-Nassar
Address: Imperial College Trials Unit & Division of Surgery
1st Floor, Stadium House, 68 Wood Lane, London W12 7RH
Tel: 0207 594 3424
Email: n.klimowska@imperial.ac.uk

Senior Statistician

Name: Dr Francesca Fiorentino
Address: Imperial College Trial Unit & Department of Surgery and Cancer
Queen Elisabeth the Queen Mother Building (10th Floor/1091) St Mary's Hospital
Imperial College London, Praed Street, London, W2 1NY
Tel: 0203 312 3761

Co-Investigators

Lead Co-Investigator
Name: Mr Taimur Shah
Address: Room 5L15, 5th Floor, Laboratory Block, Charing Cross Hospital Campus, Imperial College London, Fulham Palace Road, London W6 8RF
Urology Academic Research Fellow and Specialist Trainee
Tel: +44(0)7713 245739
Email: t.shah@imperial.ac.uk

Dr Mirella Longo
Division of Population Medicine, Cardiff University
LongoM1@cardiff.ac.uk

Professor Ann-Marie Nelson
Marie Curie Research Centre, Cardiff University
NelsonA9@cardiff.ac.uk

Mr Matthew Sydes
MRC Clinical Trials Unit at UCL, University College London
m.sydes@ucl.ac.uk

Professor John Staffurth
School of Medicine, Cardiff University
StaffurthJN@cardiff.ac.uk

Dr Zsuzsanna Tabi
Division of Cancer and Genetics, Cardiff University
tabiz@cf.ac.uk

Mr Chris Dobbs
Patient and Public Representative
chris@cd1mages.com

Mr Tim Dudderidge
Department of Urology, University Hospital Southampton NHS Trust, Southampton
timdudderidge@doctors.org.uk

Mr Stuart McCracken
Northern Institute for Cancer Research, Newcastle University
stuart.mccracken@ncl.ac.uk

Professor Toby Prevost

Imperial Clinical Trials Unit, School of Public Health, Imperial College London
a.prevost@imperial.ac.uk

Mr Mathias Winkler
Division of Surgery, Imperial College London and Department of Urology, Imperial College Healthcare NHS Trust
mathias.winkler@nhs.net

This protocol describes the CHRONOS study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken when drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the study coordination centre.

This trial will adhere to the principles outlines in the Medicines for Human Use (Clinical Trial) Regulations 2004 (SI 2004/1031), amend regulation (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Abbreviations

AE	Adverse Event
CEA	Cost Effectiveness Analysis
CI	Chief Investigator
CRF	Case Reporting Form
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
FFS	Failure Free-Survival
FT	Focal Therapy
GCP	Good Clinical Practice
HIFU	High Intensity Focussed Ultrasound
HRA	Health Research Authority
ICTU	Imperial Clinical Trials Unit
IMP	Investigational Medicinal Product
mpMRI	Multi-parametric Magnetic Resonance Imaging
NIHR	National Institute for Health Research
PET	Positron Emission Tomography
PFS	Progression Free Survival
PH	Proportional-Hazards
PIC	Patient Identification Centre
PIS	Patient/Participant Information Sheet
PPI	Patient and Public Involvement
PROMs	Patient Reported Outcome Measures
PSA	Prostate Specific Antigen
QA	Quality Assurance
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RMST	Restricted Mean Survival Time
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard-Of-Care
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

Keywords:

prostate cancer, non-metastatic, radiotherapy, prostatectomy, High Intensity Focused Ultrasound (HIFU), cryotherapy. Multi-arm multistage

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TRIAL SUMMARY

TITLE	**C**omparative **H**ealth **R**esearch **O**utcomes of **NO**vel **S**urgery in prostate cancer
AIM	To deliver an overarching RCT framework to efficiently evaluate novel surgical techniques in the treatment of non-metastatic prostate cancer **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
PHASE	Phase II Randomised Control Trial (RCT) incorporating an internal pilot
DURATION	Pilot: Recruitment 12 months. Minimum 3 months follow-up. Total 15 months. Main study: Recruitment further 48 months. Total including follow-up = 96 months
DESIGN	***Randomised controlled trial*** Two linked RCTs with CHRONOS-A and CHRONOS-B discussed with patients and choice of A or B dependent on physician and patient equipoise. - CHRONOS-A Two arm RCT - CHRONOS-B Multi-Arm Multi-Stage (MAMS) Randomised Control Trial

SAMPLE SIZE	**Feasibility/pilot** CHRONOS-A 60 patients over 12-months (These participants will form part of the main study if feasibility is met and funding obtained) CHRONOS-B 60 patients over 12-months (These participants will form part of the main study if feasibility is met and funding obtained) **Main study** CHRONOS-A 1190 patients CHRONOS-B A three-arm MAMS RCT would require 1260 patients
FEASIBILITY AND PILOT STUDY OBJECTIVES	To assess the feasibility of a trials framework that fits with existing patient and physician equipoise so that we can successfully and efficiently answer the next generation of research questions to evaluate medium-term outcomes following minimally invasive focal therapy in the treatment of clinically significant, non-metastatic prostate cancer. The embedded internal pilot objectives are: • To determine patient acceptance to randomisation. • To conduct an embedded qualitative study of patient and clinician acceptance and experience of the linked RCT CHRONOS design. • To establish the feasibility of an economic evaluation alongside the main trial. • To determine acceptability and completeness of resource use and utility measures (EQ-5D-5L). • To identify the relevant NHS and non-NHS resource use to be collected alongside the main trial. • To identify the relevant items to populate the Cost and Consequences framework. • To perform preliminary analysis of pattern of missing data.
MAIN STUDY PRIMARY OBJECTIVES	**CHRONOS-A** To evaluate PFS rates of focal therapy alone compared to radical therapy (radiotherapy or surgery) in the treatment of non-metastatic clinically significant prostate cancer. **CHRONOS-B** To evaluate FFS rates of focal therapy alone compared to focal therapy combined with other therapies as a neoadjuvant and/or adjuvant strategy.
MAIN STUDY SECONDARY OBJECTIVES	**Disease control** Determine the histological, biochemical and oncological disease control for men undergoing radical therapy, focal therapy or focal therapy with neo/adjuvant treatments. **Adverse events and Functional Outcomes** Determine the adverse events and functional outcomes after radical therapy, focal therapy or focal therapy with neo/adjuvant treatments **Health economics**

	• To establish the NHS costs of the different interventions. • To determine the Cost per QALYs (CUA), cost per PFS/FFS (CEA) and cost and consequences (CCA). • To determine acceptability and completeness of resource use and utility measures (EQ-5D-5L). **Qualitative** • Patient experience of consent and recruitment, including reasons for declining participation. • Participants' motivation to accept randomisation to and compliance with an intervention, which may or may not include neoadjuvant and adjuvant treatments. • Patients' understanding and experience of each trial arm. • Patients' experience of toxicities, focusing on erectile dysfunction and urinary symptoms. • Patients' attitudes to the predicted survival rate. • Potential improvements to recruitment processes. • Healthcare professionals' attitudes to intervention arms and trial design and whether this might impact on recruitment. **Biobank and databank objectives** • To evaluate cancer infiltrating immune cells and immune gene signatures following ablation. • 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	**Inclusion** • Histologically confirmed prostate adenocarcinoma. • PSA </=20ng/ml. • Patients must have 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 diagnostic MRI (for clinical or other reasons), a transperineal template mapping biopsy using a 5-10 mm sampling frame will be required. • 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. • Patients with bilateral histologically proven prostate cancer are permissible provided the following criteria are met: - The index lesion to be treated, if focal therapy is used, meets the above histological criteria. - The patient may have a PIRADS or Likert score 3, 4, 5 mpMRI lesion in the same hemi-gland (either right/left or anterior/posterior) as the histological index lesion. - Secondary areas of Gleason 3+3=6 of </=5mm cancer outside of the treatment field can be monitored, if present, and the patient undergoes focal therapy. - 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 with confirmation of the presence of inflammation or atrophy, if the patient is to undergo focal therapy*. • Radiological stage T2b/T3a will require central review regarding suitability for focal therapy.

	• 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**. • Age at least 18 years of age. • 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. **Exclusions** • Previous or current LHRH agonist or LHRH antagonist or anti-androgen use in CHRONOS-B. • 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). • Previous treatment for prostate cancer. • Life expectancy likely to be less than 10 years. • Unable to give informed consent.
STUDY PROCEDURES	**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 5mg once daily for a minimum of 12 weeks followed by focal therapy (as per control arm). • Arm 3 (Intervention): Neoadjuvant bicalutamide 50mg 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.

FEASIBILITY AND PILOT STUDY ENDPOINTS	**CHRONOS-A and CHRONOS-B Pilot Outcome Measures** **Primary** • Feasibility and acceptance of randomisation (rate per -month, per -centre averaged) and compliance to allocated arm. **Secondary** • Patients' experience of consent and recruitment, including reasons for declining participation. • Patients' motivation to accept randomisation to, and compliance with an intervention and understanding of each trial arm. • Patients' experience of each arm including systemic issues, erectile dysfunction, urinary symptoms and rectal symptoms. • Healthcare professionals' attitudes to intervention arms and trial design and whether this might impact on recruitment. • Proportion of patients successfully recruited into each of CHRONOS-A and CHRONOS-B • Potential improvements to recruitment processes. • To establish the feasibility of an economic evaluation alongside the main trial.
PRIMARY ENDPOINTS (Main Stage)	**CHRONOS-A:** 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. **CHRONOS-B:** 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.
SECONDARY ENDPOINTS (Main Stage)	**Disease control** • 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). • Rates of second or third focal therapy sessions, in-field or out-of-field • Rates of radiotherapy as adjuvant or salvage therapy following surgery or focal therapy. • Rates of prostatectomy as adjuvant or salvage therapy following radiotherapy or focal therapy. • Rates of systemic therapy as adjuvant or salvage therapy following surgery, radiotherapy or focal therapy. • Rates of prostate cancer-specific mortality. • Rates of all-cause mortality. • Long-term health outcomes of those participants consenting to longitudinal follow-up will be reported in subsequent studies pending further funding. **Adverse events and functional outcomes** • Rates of cystoscopic interventions following treatment. • Rates of implant insertion for treatment of incontinence and erectile dysfunction. • Rates of medication and/or pump devices used for erectile dysfunction following treatment. • Rates of endoscopic investigations of the lower bowel following treatment. • Rates of pad-use and quantity per day for urinary incontinence following treatment. • Rates of pad-use and quantity per day for faecal incontinence following treatment. • Rates of adverse event rates and complications.

	• Genito-urinary and rectal side-effects using patient-reported outcome measures using validated questionnaires (EQ-5D-5L, International Index of Erectile Function-15, EPIC-26, EPIC Urinary domain, International Prostate Symptom Score and CTCAEv4.0 bowel domain) including evaluation of return to baseline function for erectile and urinary function and various minimum decreases in PROMS scores as defined for IIEF and IPSS in the literature that might be clinically relevant. **Health economics** • To establish the NHS costs of the different interventions. • To determine the incremental cost per quality adjusted life year (QALYs) gained over the estimated lifetime of participants for focal therapy versus radical therapy. • To determine the incremental cost per quality adjusted life year (QALYs) gained over the estimated lifetime of participants for focal therapy versus focal therapy with neoadjuvant and/or adjuvant strategies. **Qualitative** • The impact on participants' overall health-related quality-of-life including adverse events and impact on genito-urinary and rectal functional status using validated patient reported outcome measures. • 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 in CHRONOS-A and CHRONOS-B. **Translational, Biobank and Databank** • Analysis on the localisation and nature of cancer-infiltrating immune cells and the immune-relevant gene expression within the cancer tissue. • The creation of a biobank and databank of matched blood, serum, plasma and pre-digital rectal examination urine as well as imaging as well as FFPE biopsy samples.

1. BACKGROUND

1.1 Clinical setting

Over 47,000 men were diagnosed with prostate cancer in 2015 in the UK; this is expected to rise to over 60,000 by 2030 [1]. Many have early cancer that has not spread and are often treated with radical surgery or radical radiotherapy. These treatments target the whole prostate regardless of size or burden of cancer within the prostate. Whilst radical treatments are effective, side-effects are well recognised, with incontinence in 10-20% and impotence in 30-60%; radiotherapy can also cause back passage symptoms (bleeding, discomfort, loose stools) in 5-10% (moderate to severe). This is because nerves, blood vessels and other tissues surrounding the prostate sometimes get damaged. Further to the described side effects, radical therapies have an approximate failure rate of 10-15% at 5-years following treatment [2-7].

There has been an increasing recognition that many low risk cancers do not progress and do not require treatment [8]. A number of randomised trials have demonstrated no difference between radical therapy and active monitoring in low risk disease, although most have shown that intermediate and high risk cancers do benefit from treatment [5]. Therefore, it is widely accepted that treatment should be given to these two groups of patients with clinically significant prostate cancer and low risk clinically insignificant prostate cancer placed on active surveillance and treated only if signs of progression occur [5]. We, and others, have questioned the attribution of a cancer diagnosis to such entities [8].

Over the last 10 years, we and others have conducted a phased evaluation of a novel treatment for prostate cancer called focal therapy (FT), using HIFU (heating) and cryotherapy (freezing), which can be delivered as a minimally invasive, day-case procedure. Focal therapy involves either heating or freezing only specific areas of the prostate involving clinically significant prostate cancer and not the entire gland. In most other cancers, the tumour alone, rather than the whole organ, is targeted if possible; such examples include kidney, liver, thyroid, skin, bladder, and breast cancer. Advances in imaging now allow us to target only those areas of the prostate containing cancer. When carried out in the prostate, there is a reduced risk of genito-urinary and rectal side-effects; incontinence (1-2%), erectile dysfunction (5-15%) and 0.1% rectal problems. These are much lower than the reported side-effects seen from radical surgery (erectile dysfunction 30-60%, incontinence 5-20%) or radiotherapy (erectile dysfunction 50-60%, urinary dysfunction 5-20% and rectal toxicity 5-10%)[12].

Although cancer-specific survival is >99% at 5-years following FT, 1 in 5 need a further FT session to the same area and 1 in 10 overall still require whole-gland or systemic therapy [9-13]. A recent systematic review demonstrated that the rate of a second FT in 3,230 men, treated over the last 10 years, was ~15%, but with a low side-effect profile. The majority had intermediate risk cancer that most would deem clinically significant [14]. A recent RCT compared FT using vascular-targeted photodynamic therapy to active surveillance in 413 men with very low risk cancer and showed that biopsy upgrading was reduced in the FT arm [15]. However, we and many others do not believe that FT should be used in men with low-risk disease; indeed, the UK Focal Therapy User Group has advocated its members do not treat low-risk cancers.

To date, approximately 90% of FT cases in the UK are intermediate or low-volume high-risk cancers. There is currently no evidence comparing FT to standard of care active treatments such as radiotherapy or prostatectomy in men with clinically significant cancer. A recently completed pilot RCT comparing FT to prostatectomy (called PART) 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 FT arm. We previously reviewed 12 RCTs in which very different interventions in localised prostate cancer were compared, but failed to accrue. We proposed that there was a need to ensure novel trial designs that embrace clinical and patient equipoise [16].

In addition to the need for RCTs comparing FT against standard care with radical radiotherapy/prostatectomy, there clearly needs to be a deeper understanding as to why failure occurs after FT and to develop strategies to reduce the need for further treatment. Failure can occur due to, a) heat-sink effects countering thermal effects, b) swelling during treatment causing skip-lesions or, c) progressive/de-novo out-of-field development of significant cancers. Strategies that decrease neovasculature, reduce tumour volume, or potentiate the immune response induced by ablation might complement FT to reduce failure [16-28]).

If FT fails it can be redone to the same area; an attribute that is missing from radical therapies. If redo FT fails, then men can still proceed to radical therapy. Over a 5-year median follow-up, redo FT rates are approximately 20-30% and salvage radical or systemic therapy occurs in 10%. Metastases are uncommon (3%) and cancer-specific survival 100% over the same period of time [10]. By comparison, the reported failure rate requiring further treatment after radical therapy is about 10-20% over a 5-10 years median follow-up. Currently 4-5% of cases have out-of-field failure at a median of 5 years [29], which might represent progression or may represent the false-negative rates of mpMRI and biopsy used to localise disease prior to focal therapy. Although many patients accept these rates of further treatments after FT, there is a need to investigate strategies that might optimise FT further to reduce patient and healthcare burden.

In some other cancer treatments, various additional treatments are given in combination to treating the tumour selectively. For instance, in breast cancer, radiotherapy is used in low doses to treat the rest of the breast after lumpectomy to reduce cancer recurrence. Another example is prostate cancer radiotherapy, where hormones given before and after radiotherapy have been shown to improve cancer control, compared to radiotherapy alone or hormones alone.

Out with surgical expertise and learning curve for carrying out the procedure, failure after FT can occur due to a number of mechanisms that might be modified using neoadjuvant and adjuvant strategies:

- The vasculature of the tumour prevents complete ablation by causing sub-optimal ablative effect (heat-sink or heat wash-out effects).
- Satellite areas of cancer a few millimetres away from the main targeted lesion, but not detected with MRI or biopsy and outside the normal applied margin of 5mm of ablation, may be left untreated (margin effect).
- Untreated prostate tissue might harbour clinically significant lesions, missed by MRI and biopsy, which then progress or micro-metastasise (staging effect).
- Untreated prostate tissue might develop de novo clinically significant cancers not present at time of diagnosis (field effect).

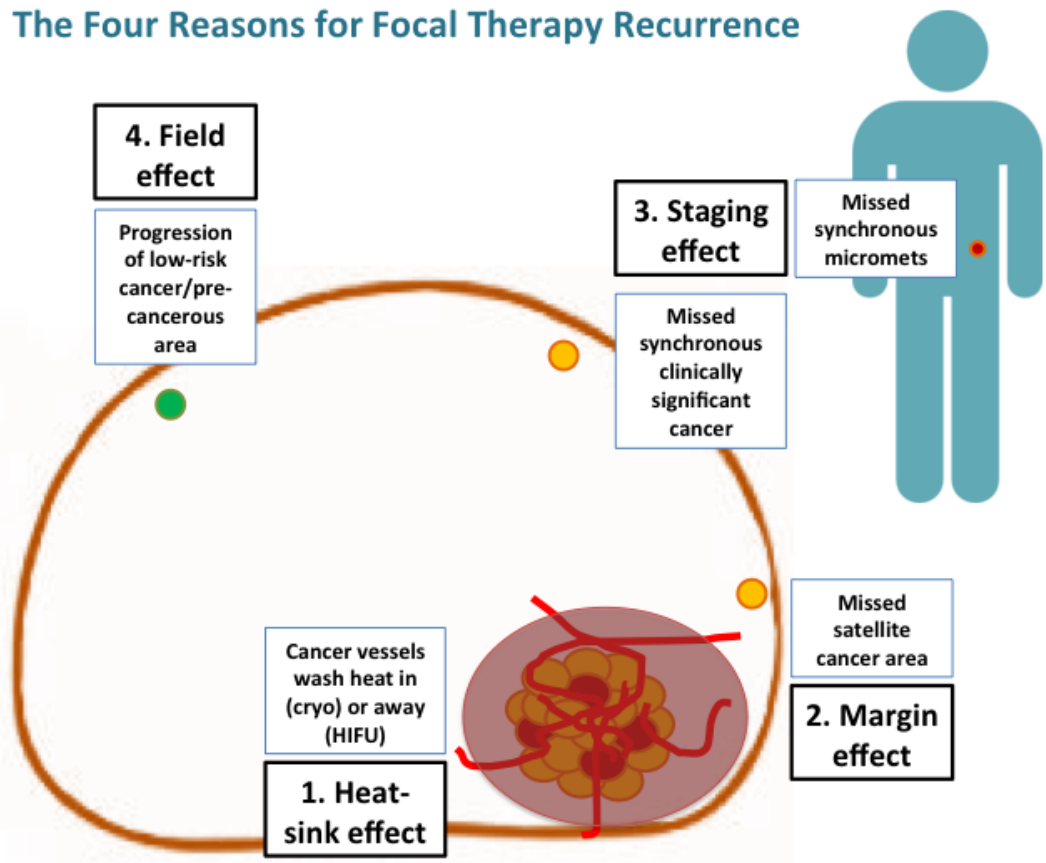


Figure 1. *FT failure can occur due to a number of modifiable mechanisms:*
1. Tumour vasculature can prevent adequate ablative temperatures (heat sink).
2. Large tumours can swell and satellite cancer might be left untreated (margin effect).
3. Untreated prostate might harbour clinically significant lesions, missed by MRI and biopsy, which then progress (staging error).
4. Untreated prostate might develop de novo significant cancers (field effect).

1.2 Rationale for CHRONOS

The current therapeutic ratio for radical therapy is not ideal with a significant side-effect profile for what is arguably a small cancer-specific survival benefit at 10-years of 5% [2-5, 9]. We have shown in several hundred consecutively-treated, self-selecting men treated using FT with HIFU or cryotherapy (n=760) that cancer survival at a median of 5-years is high (100%) and is complemented by a low side-effect profile. Re-treatment FT is, however, needed in 20% and radical whole-gland therapy in 10% [10-13]. These data seem comparable to standard care treatments but are based on non-randomised prospective series.

Our Comparative Health Research Outcomes of Novel Surgery in prostate cancer (CHRONOS) proposal aims to conduct randomised comparative trials that might deliver level 1 evidence on FT outcomes in men with clinically significant prostate cancers. CHRONOS aims to test the feasibility and pilot stages of two parallel RCTs within an overarching strategy that fits with existing patient and physician equipoise and maximizes the chances of success and potential benefit to patients and healthcare services.

We will conduct a head-to-head RCT comparing FT to radical radiotherapy/ prostatectomy (CHRONOS-A). Most centres do not offer FT and therefore, we will test what levels of equipoise exist in those UK centres that do or don't offer FT.

Further, as FT is already offered in a number of 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, an RCT that might have potential to improve outcomes for these men in the future. Therefore, in parallel to CHRONOS-A, in those who express a strong preference for FT, we will conduct the first surgical multi-arm, multi-stage RCT (CHRONOS-B). This will compare FT alone to FT combined with different neoadjuvant agents to determine whether failure can be improved with these additional treatments. As FT failure is related to skip-lesions caused by swelling and heat-sink effects as well as progressive or de-novo clinically significant cancers occurring in untreated prostate tissue, we hypothesise that strategies to decrease neovasculature and reduce tumour volume might improve the ablative effect on cancer cells. Participation into CHRONOS-A or CHRONOS-B will be determined by participant and physician preference and discussion.

We plan to consider a number of neoadjuvant strategies in CHRONOS-B that make mechanistic sense in potentially working alongside FT. Hormonal therapy cytoreduces cancers and decreases vascularity thus minimising the heat-sink effect that counteracts ablation. In the future, immune-modulators might potentiate the known immune responses that occurs secondary to ablation. Metabolic agents such as metformin and low-dose cyclophosphamide are other possibilities. Our proposal for a feasibility study aims to initially test two commonly used hormonal agents alongside focal therapy. Our initial research arms in CHRONOS-B will use Finasteride (5-alpha reductase inhibitor) or bicalutamide (anti-androgen) for 12-weeks before FT. Additional arms can be tested in future (e.g., immunotherapeutic agents, checkpoint-inhibitors, low-dose cyclophosphamide and other hormone treatments [abiraterone, enzalutamide, apalutamide]). The full trial would be designed with this in mind.

CHRONOS is similar, albeit not equivalent, to the strategy used in PACE-A and PACE-B in testing 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. Thus, the loss of eligible patients would be minimal and would likely maintain a high recruitment rate overall. As the main concern with running any such study is patient acceptance of the design and compliance we are initially conducting an internal pilot/feasibility study. A full sample size calculation for both the pilot and for the main stages has been provided below nonetheless so that if funding were available, we would seamlessly run into the main stage of the CHRONOS.

One concern with such a design is that there may be an unrecognised selection bias with patients choosing which randomisation to enter. As no direct comparisons will take place between CHRONOS-A and CHRONOS-B the impact of this should be minimised. In addition, we will assess the demographics of those eligible patients who refused randomisation. In reality, such a design reflects what commonly occurs in clinical practice and is therefore a more pragmatic design. Another concern is clinician bias to one specific randomisation. We aim to minimise this by consent workshops, training sessions and through a quality control process that is integrated to the qualitative work. As a surgical RCT, there can be challenges in conduct and delivery so it is important that qualitative research incorporating recorded

interviews to explore issues qualitatively amongst those patients who accept the trial, patients who turn down the trial, and patients that had low compliance in comparison with another subgroup that had high compliance (in each arm). Physicians and nurses will also be interviewed on their levels of equipoise, acceptability of trial design and interventions. The qualitative work will guide changes to the recruitment strategy as well as patient information (verbal/written).

Improving understanding of biological and mechanistic processes

We will conduct hypothesis-generating analyses on the localisation and nature of cancer-infiltrating immune cells and the immune-relevant gene expression within the cancer cells. The results will be extremely valuable by allowing a better understanding of the genetic and immunological landscape in prostate cancer and the interactions with ablative modalities and neoadjuvant strategies.

1.2.1. Investigational Agents: Rationale for Neoadjuvant and Adjuvant Interventions in CHRONOS-B

This protocol aims to test a number of neoadjuvant and/or adjuvant strategies, in combination with FT, within a multicentre, phase II, multi-arm, multi-stage randomised controlled trial. We hypothesize that use of these biologic effects 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. The strategies available to us are numerous. First, hormonal therapies (5-alpha reductase inhibitors, LHRH agonists, anti-androgens, other novel hormonal agents [enzalutamide, abiraterone, apalutamide]), which reduce tumour size, reduce/eliminate small low-grade tumours as well as reduce vasculature, might complement focal ablation by reducing the heat-sink and margin effects. Second, as ablation induces an immune response, immuno-modulatory agents that might potentiate this 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.

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. 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.

1.3 Aims

To deliver an overarching RCT framework to efficiently evaluate novel surgical techniques in the treatment of non-metastatic prostate cancer

<u>CHRONOS-A</u>

Pilot: To determine if men will agree to participate in an RCT that randomly assigns them to FT alone or radical therapy (radiotherapy or prostatectomy).

Main: To determine if FT 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 FT will agree to participate in a multi-arm, multi-stage (MAMS) RCT that randomly assigns them to FT alone or FT in combination with neoadjuvant and/or adjuvant agents.

Main: To determine if FT combined with neoadjuvant and/or adjuvant agents compared to FT alone will improve overall failure-free survival (FFS), in men with clinically significant non-metastatic cancer

1.3.1 CHRONOS-A

CHRONOS-A is an open-label Phase II/III non-inferiority RCT comparing standard care radical therapy with FT alone.

1.3.2 CHRONOS-B

To our knowledge this is the first application of a MAMS RCT to a surgical intervention in all arms. We plan to consider a number of neoadjuvant and/or adjuvant strategies that make mechanistic sense, such as hormonal therapy (which cytoreduce tumours and reduce heat-sink effect) or immune-modulation (potentiate existing immune responses that occur secondary to ablative therapies). The MAMS design is adaptive, allowing comparison of multiple research arms with a common control arm and incorporating the pilot and effectiveness stages, so that arms can be dropped or added depending on pre-planned interim analyses. In other words, a pre-planned interim analysis for an intermediate primary outcome measure allows the closure of any research arm which does not promise on efficacy and additional arms can be added in the future without the need for a whole new trial. The control arm recruits throughout, whilst only research arms that meet the interim a priori outcome threshold(s) will continue. This is an efficient design in terms of patient numbers because the control arm patients form the control for all intervention arms as opposed to running several head-to-head 2-arm RCTs. In essence, a smaller overall number of patients are needed, fewer resources are used and research questions are answered in a timely fashion.

1.4 Risk/Benefit Assessment

CHRONOS-A
Risks: Some centres may not be equipped with facilities to provide FT or radical therapy, and therefore patients may need to travel to another hospital site. This is what currently happens in clinical practice. Side effects associated with focal therapy include incomplete treatment of the index lesion, and anxiety related to this. Further, it is expected that 1 in 5 patients that undergo focal treatment will require a repeated procedure within 5 years of treatment. Risks associated with radical treatment include urinary incontinence, erectile dysfunction, bowel problems, significant bleeding, urethral stricture, bowel strictures and side-effects from hormonal therapy such as loss of libido, hot flushes and breast tenderness. Men who undergo radical radiotherapy may require pre-procedure intervention to manage pre-existing lower urinary tract symptoms.

Benefits: Men undergoing focal therapy can expect a lower likelihood of developing urinary incontinence, erectile dysfunction, bowel problems and shorter post-treatment recovery time relative to those undergoing radical treatment. Those undergoing radical treatment should have less anxiety regarding incomplete treatment of their cancer and follow up for disease relapse is likely less burdensome to healthcare provider and patient.

CHRONOS-B
Risks: Men randomised to the focal therapy and neoadjuvant treatment arm may experience side effects from the neoadjuvant therapy, which can include weight gain, decreased libido, breast tenderness, gynaecomastia and hair loss.

Benefits: The time in which men require repeat focal therapy, or salvage/ whole gland therapy is hypothesised to increase with the use of neo-adjuvant treatments, with fewer significant side effects as observed in the radical therapy treatment arm.

2. OBJECTIVES AND ENDPOINTS

2.1 Feasibility and Pilot Objectives

To deliver a trials framework that fits with existing patient and physician equipoise so that we can successfully and efficiently answer the next generation of research questions to evaluate medium-term outcomes following minimally invasive focal therapy in the treatment of clinically significant non-metastatic prostate cancer.

The embedded internal pilot objectives are:

- To determine patient acceptance to randomisation, measured using rates of accrual and compliance, to CHRONOS-A, which will randomly assign men to either focal therapy alone or radical therapy (radiotherapy or surgery).
- To determine patient acceptance to randomisation, measured using rates of accrual and compliance, to a MAMS RCT called CHRONOS-B, which will randomly assign men to focal therapy alone or focal therapy in combination with neoadjuvant and/or adjuvant strategies that might improve ablative efficacy.
- To conduct an embedded qualitative study of patient and physician acceptance and experience of the parallel CHRONOS design for this surgical intervention and determine strategies to optimize recruitment and compliance following randomisation.
- To establish the feasibility of an economic evaluation alongside the main trial.
- To determine acceptability and completeness of resource use and utility measures (EQ-5D-5L).To identify the relevant NHS and non-NHS resource use to be collected alongside the main trial.
- To identify the relevant items to populate the Cost and Consequences framework.
- To perform preliminary analysis of pattern of missing data.

2.2 Main Study Primary Objectives

CHRONOS-A
To evaluate progression-free survival (PFS) rates of focal therapy alone compared to radical therapy (radiotherapy or surgery) in the treatment of non-metastatic clinically significant prostate cancer. PFS is defined as time from randomisation to salvage whole-gland or systemic therapy, prostate cancer metastases or prostate cancer-specific mortality.

CHRONOS-B

- To evaluate Failure-Free-Survival (FFS) rates of focal therapy alone compared to focal therapy combined with other therapies as a neoadjuvant strategy. FFS is defined as time from randomisation to further focal therapy session or salvage whole-gland or systemic therapy or prostate cancer metastases or prostate cancer-specific mortality.

2.3 Main Study Secondary Objectives

Disease control

- Determine the histological, biochemical and oncological disease control for men undergoing radical therapy, focal therapy alone or focal therapy with neo/adjuvant treatments.

Adverse events and Functional Outcomes

- Determine the adverse events and functional outcomes after radical therapy, focal therapy alone or focal therapy with neo/adjuvant treatments.

Health economics

- To establish the NHS costs of the different interventions.
- To determine the cost per QALYs (CUA), cost per PFS/FFS (CEA) and cost and consequences (CCA) to inform the decision regarding which arm is most appropriate.
- To determine acceptability and completeness of resource use and utility measures (EQ-5D-5L).

Qualitative

- Patient experience of consent and recruitment, including reasons for declining participation.
- Participants' motivation to accept randomisation to and compliance with an intervention, which may or may not include neoadjuvant and adjuvant treatments.
- Patients' understanding and experience of each trial arm.
- Patients' experience of toxicities focusing on erectile dysfunction, urinary symptoms and rectal symptoms.
- Patients' attitudes to the predicted survival rate.
- Potential improvements to recruitment processes.

Biobank and databank objectives

- To build a biobank and databank of matched blood, serum, plasma and pre-digital rectal examination urine as well as imaging as well as FFPE biopsy samples (diagnostic samples before entry into trial and subsequent prostate, prostatectomy, and distant site samples carried out post-treatment) will be built for future validation and development of other biomarker panels as well as educational purposes. To be carried out prior to treatment and at defined points after treatment.

2.4 Feasibility and Pilot Endpoints

CHRONOS-A and CHRONOS-B Pilot Outcome Measures

Primary

- Feasibility and acceptance of randomisation (rate per-month per-centre averaged) and compliance to allocated arm.

Secondary

- Patients' experience of consent and recruitment, including reasons for declining participation.
- Patients' motivation to accept randomisation to, and compliance with an intervention and understanding of each trial arm.
- Patients' experience of each arm including systemic issues, erectile dysfunction, urinary symptoms and rectal symptoms.
- Healthcare professionals' attitudes to intervention arms and trial design and whether this might impact on recruitment.
- Potential improvements to recruitment processes.
- To establish the feasibility of an economic evaluation alongside the main trial.

Feasibility will be measured based on a point-estimate of recruitment rates. Eligibility will be assessed against pre-defined eligibility criteria. The reasons for ineligibility will be recorded and compared across CHRONOS-A and CHRONOS-B. The retention/compliance rate will be defined as the number of participants completing study interventions and any follow-up imaging and biopsy. The reasons for withdrawal will be documented with a questionnaire given to individuals.

The integrated qualitative component is designed to inform the primary and secondary trial objectives in the trial recruitment and testing stages. Participant interview data highlighting trial processes in need of improvement may be used in real time to allow timely protocol amendments in order to improve recruitment and retention of participants. We will also interview healthcare professionals (physicians, nurses) responsible for recruiting patients.

2.5 Main Study Primary Endpoints

CHRONOS-A
Progression-Free Survival (PFS) with progression defined as biochemical failure (radical therapies only), salvage therapy (local or systemic) or prostate cancer metastases or prostate cancer specific mortality. 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 an event.

CHRONOS-B
Failure-Free survival (FFS) with failure defined as time to one further focal therapy session or salvage therapy (local radiotherapy or surgery, or systemic) or prostate cancer metastases or prostate cancer specific mortality.

2.6 Main Study Secondary Endpoints

Disease control
- Rates of positive biopsy for any cancer and significant cancer defined by a number of different thresholds on biopsy following focal therapy (treated and untreated side).
- Rates of second or third focal therapy sessions, in-field or out-of-field.
- Rates of radiotherapy as adjuvant or salvage therapy following surgery or focal therapy.
- Rates of prostatectomy as adjuvant or salvage therapy following radiotherapy or focal therapy.
- Rates of systemic therapy as adjuvant or salvage therapy following surgery, radiotherapy or focal therapy.
- Rates of prostate cancer-specific mortality.

- Rates of all cause mortality.
- Long-term health outcomes of those participants consenting to longitudinal follow-up will be reported in subsequent studies pending further funding.

Adverse events and functional outcomes
- Rates of cystoscopic interventions following treatment.
- Rates of implant insertion for treatment of incontinence and erectile dysfunction.
- Rates of medication and/or pump devices used for erectile dysfunction following treatment.
- Rates of endoscopic investigations of the lower bowel following treatment.
- Rates of pad-use and quantity per day for urinary incontinence following treatment.
- Rates of pad-use and quantity per day for faecal incontinence following treatment.
- Rates of adverse event rates and complications.
- Genito-urinary & rectal side-effects using patient-reported outcome measures using validated questionnaires (EQ-5D-5L, International Index of Erectile Function-15, EPIC-26, EPIC Urinary domain, International Prostate Symptom Score and CTCAEv4.0 bowel domain) including evaluation of return to baseline function for erectile and urinary function and various minimum decreases in PROMS scores as defined for IIEF and IPSS in the literature that might be clinically relevant.

Health economics
- To establish the NHS costs of the different interventions.
- The incremental cost per quality adjusted life year (QALYs) gained over the estimated lifetime of participants for focal therapy versus radical therapy.
- The incremental cost per quality adjusted life year (QALYs) gained over the estimated lifetime of participants for focal therapy versus focal therapy with neoadjuvant strategy.

Qualitative
- The impact on participants' overall health-related quality-of-life as well as adverse events and impact on genito-urinary and rectal functional status using validated patient reported outcome measures.
- 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 in CHRONOS-A and CHRONOS-B.

Imaging and Pathology
- Accuracy and variability of multi-parametric MRI in detecting disease at baseline prior to focal therapy and absence or presence of recurrence of cancer based on histology outcomes on biopsy. Target definition for recurrence will be defined as significant prostate cancer as per inclusion criteria.

Translational, Biobank and Databank
- Analysis on the localisation and nature of cancer-infiltrating immune cells and the immune-relevant gene expression within the cancer tissue.
- The creation of a biobank and databank of matched blood, serum, plasma and pre-digital rectal examination urine as well as imaging as well as FFPE biopsy samples (diagnostic samples before entry into trial and subsequent prostate, prostatectomy, and distant site samples carried out post-treatment) will be built for future validation and development of other biomarker panels as well as educational purposes. To be carried out prior to treatment and at defined points after treatment.

2.7 Summary Table of Objectives and Endpoints

Study stage	Objectives	Endpoints	Time-point(s) of evaluation of this endpoint (if applicable)
Pilot	**Primary**	As above	At time of consent (acceptance to randomisation) and at time to treatment (compliance)
Pilot	**Secondary**	As above	At time of consultation for study, after consent and after treatment with a minimum follow-up of 3 months after randomisation
Main (if funded)	**Primary**	As above	At time of progression or failure judged clinically or maximum 5 years follow-up after randomisation
Main (if funded)	**Secondary**	As above	Up to and including 5 years from randomisation

3. STUDY DESIGN

CHRONOS will be performed at UK and potentially international sites if funding for the main trial is secured. This is a randomised, unblinded multicentre study, including two parallel randomised controlled trials, with comparison against standard care. Within CHRONOS-A, subjects will be randomised to either control (standard care radical therapy) or focal therapy. Within CHRONOS-B, focal therapy will be delivered, and subjects further randomised to receiving neoadjuvant and/or adjuvant therapy.

3.1 Design

Two linked RCTs with CHRONOS-A and CHRONOS-B will be discussed with patients and the choice of A or B dependent on physician and patient equipoise.

- CHRONOS-A: Two arm RCT
- CHRONOS-B: Multi-Arm Multi-Stage (MAMS) Randomised Control Trial

Due to the nature of the study design and its interventions there will be no blinding of either the physician or patient.

Stratified randomisation will take into account the following

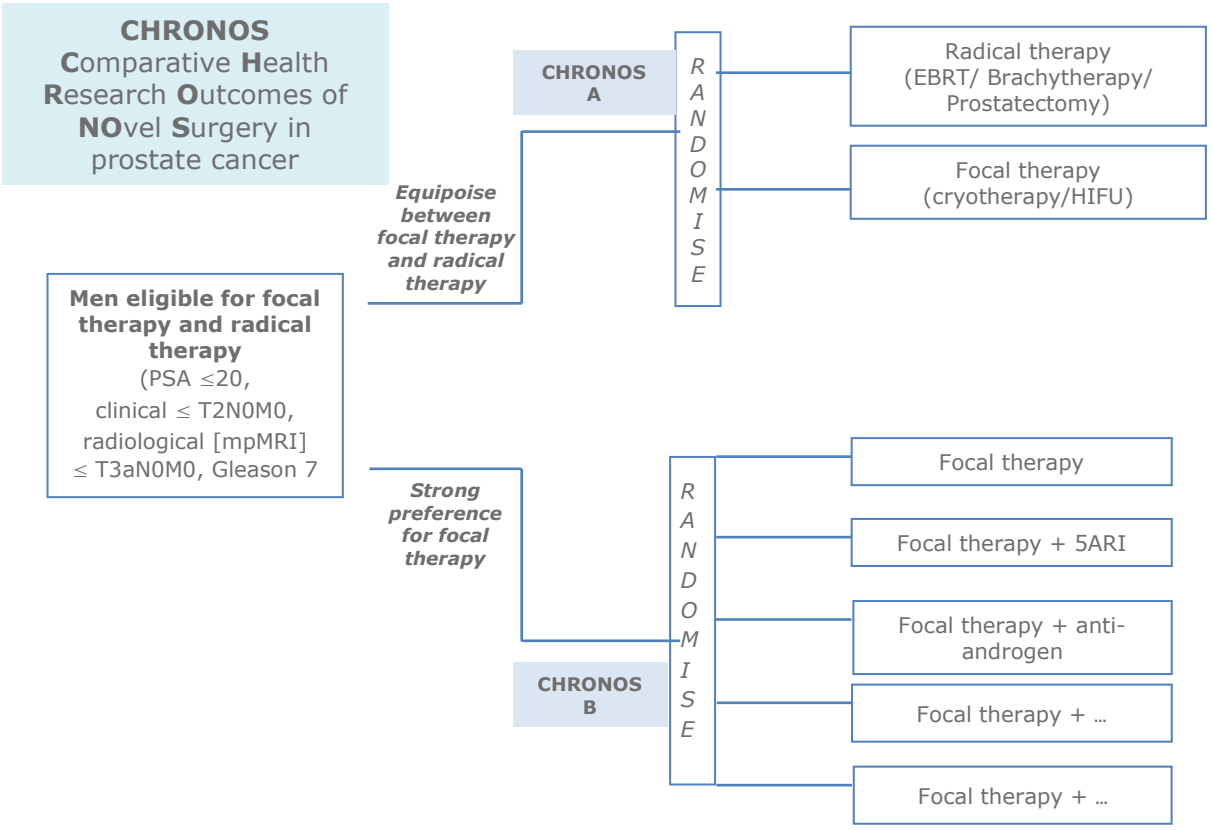
- Tumour grade (Gleason 6 [grade group 1], Gleason 7 [grade group 2], Gleason 7 [grade group 3])
- Local stage (T2 versus radiological (MRI) T3)
- CHRONOS-A only: previous or current 5-alpha reductase inhibitor use

3.2 Treatment regimens

Treatment Sequence	Number of subjects	Details
CHRONOS-A		
Control arm	Pilot: 30 Main: 595	Radical radiotherapy or radical prostatectomy (as per physician and patient decision/preference

Intervention arm	Pilot: 30 595	Focal therapy using HIFU or cryotherapy (as per physician and patient decision/preference)
Total number	Pilot: 60 Main: 1190	
CHRONOS-B		
Control arm	Pilot: 20 Main: 400	Focal therapy using HIFU or cryotherapy (as per physician and patient decision/preference)
Intervention arm 1	Pilot: 20 Main: 400	Neoadjuvant finasteride 5mg once daily for a minimum of 12 weeks followed by focal therapy (as per standard care control arm for CHRONOS-B).
Intervention arm 2	Pilot: 20 Main: 400	Bicalutamide 50mg once daily for 12 weeks followed by focal therapy (as per standard care control arm for CHRONOS-B)
Future Intervention arms …x	Pilot: Not applicable Main: 400	To be defined with substantial amendments to protocol.
Total number Without future intervention arms	Pilot: 60 Main: 1200 for 3 arms	

Figure 1: Study flowchart



4. PARTICIPANT ENTRY

4.1 Study setting and population

Men with non-metastatic prostate cancer who are suitable for focal therapy and radical therapy will be approached for recruitment into CHRONOS. These criteria reflect those we have used in 4 NCRN Phase II trials recruiting approximately 500 patients. These criteria also govern the prospective registry in the UK. Our criteria are designed to ensure suitability for focal therapy but also recruit men with clinically significant prostate cancer that clinicians would recommend for active treatment not active surveillance. Whilst there has been a lot of debate about whether men with localised prostate cancer should be treated, this proposal aims to evaluate men where there is clear consensus that treatment is required as otherwise the cancer would progress and metastasise. Focal therapy is not being proposed or used currently in the UK as an alternative to active surveillance.

Inclusion criteria (as before)

- PSA </=20ng/ml
- Patients must have 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 diagnostic MRI (for clinical or other reasons), a transperineal template mapping biopsy using a 5-10 mm sampling frame will be required
- Histologically proven prostate adenocarcinoma

- 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.
- Bilateral histologically proven prostate cancer is permissible provided the following criteria are met:
  - The index lesion to be treated if focal therapy is used meets the above histological criteria.
  - 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
  - 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.
  - 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*
- Radiological stage T2b/T3a will require central review regarding suitability for focal therapy.
- 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.
- Age at least 18 years of age
- 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.

Exclusion criteria

- Previous or current LHRH agonist or LHRH antagonist or anti-androgen use in CHRONOS-B.
- 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)
- Previous treatment for prostate cancer
- Life expectancy is likely to be less than 10 years
- Unable to give informed consent

5. PROCEDURES AND MEASUREMENTS

5.1 Identification and recruitment of patients

All men diagnosed with prostate cancer that go before a multidisciplinary team (MDT) meeting or a tumour board, as well as any man meeting the eligibility criteria prior to MDT or tumour board discussion, will be identified for screening. Members of the clinical team or MDT / tumour board will identify patients suitable for CHRONOS. The treating clinicians will mention the study and then the local research nurses/fellows or clinical trial coordinators or clinical trial practitioners, or the treating clinicians, will then approach the patient to ascertain whether they are interested. After an initial discussion, the Patient Information Sheet (PIS) for either CHRONOS-A or CHRONOS-B, or both, if appropriate, will be given or emailed or posted to the patient. Those patients already aware of their diagnosis can be approached by telephone to enquire as to their interest in the study, so that a PIS can be sent out by email or post, prior to a clinical visit. Patients will be given a minimum of 24 hours to read the PIS before consenting to participate. Each centre will be asked to keep a screening log to determine acceptability to the study and its two randomisations.

Patients who are due to discuss the trial in clinic with their clinician will be approached for participation in the embedded qualitative research. The qualitative research information sheet will be sent to them by post or email, or by hand, and if they agree, written informed consent will be taken on the day of the consultation.

Healthcare professionals participating in the study will be approached for participation in the embedded qualitative research. The qualitative research information sheet will be sent to them by post or email or by hand and if they agree, written informed consent will be taken on the day of the consultation.

We anticipate most patients will be recruited via formal recruitment sites, however if due to local resource capabilities, recruitment may also include Patient Identification Centre (PIC) sites.

5.2 Screening and pre-randomisation evaluations

Prior to enrolment all patients must have undergone standard of care (SOC) staging investigations which include a prostate multi-parametric MRI (unless contraindicated), prostate biopsy (transperineal or transrectal), and may include CT abdomen/pelvis, a chest x-ray (or CT chest) or a radioisotope bone scan (or other equivalent alternative whole body imaging including but not limited to whole-body MRI or PET-CT), as per local standard practice. Patients will need to have histologically proven localised disease within the prostate. There will be no restriction on the type of prostate biopsy used for diagnosis, unless mpMRI is not appropriate, in which case template mapping biopsies using 5-10 mm sampling will be required prior to enrolment. Written informed consent will be obtained before the subject undergoes any further screening procedures.

5.3 Randomisation

Randomisation will take place centrally via the InForm system. Randomisation will be blocked and stratified by the following stratification factors:

- 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 5ARI use

5.4 Code-breaking/ Unblinding

Not applicable. This is an open label RCT.

5.5 Integrated Qualitative Outcome Measures

The integrated qualitative component of the CHRONOS trial will explore patients with prostate cancer and their experiences and perceptions of participating in either a non-inferiority trial of focal therapy, or a second trial exploring focal therapy used alone versus focal therapy plus combinations of neoadjuvant or adjuvant agents.

The qualitative data sets will be thematically analysed for common themes in relation to real-time participant experience of trial processes and treatment protocols. The analysis will take into account spontaneously reported participant experience, which is often a reflection of idiosyncratic attitudes and personal contexts, to enable patient reported experience outcomes supplementary as secondary trial outcomes.

Additionally, participant interview data highlighting trial processes in need of improvement will be used, in real time, for presentation to TMG and TSC meetings to allow necessary protocol amendments in order to improve recruitment and retention of participants, as exemplified by ongoing Wales Cancer Trials Unit trials (ROCS: ISRCTN12376468, and SCOPE 2).

5.5.1 Embedded qualitative study aims

1. To assess patient experience and perceptions of each arm of CHRONOS-A and CHRONOS-B including,
    - Understanding and acceptability of trial processes
    - Perceptions of trial equipoise and risk/benefit assessment by participants
    - Patient reported experience of allocated interventions to inform stopping rules for trial arms of CHRONOS-B
    - Suggestions for protocol amendment based on real time patient experience
2. To examine the personal impact of treatment on patients' health and wellbeing
3. To understand patients' reasons for declining the trial
4. To understand clinical teams recruiting perceptions of equipoise in relation to the CHRONOS trial.

5.5.2. Sampling Strategy

Patients will be faced with different information, risk/benefits, motivations to participate, and decisions depending on which trial and which arm. As such, minimal size samples will be used to ensure all trial arms are represented to engage with a breadth of patient experience.

- Minimum 6 from each arm of CHRONOS-A.
- Minimum 6 from the focal therapy arm of CHRONOS-B.
- Minimum 6 from CHRONOS-B trial arms at last follow-up in pilot (patient experience of acceptable interventions, e.g. toxicities, compliance).
- Minimum 6 participants from patients that decline to enter CHRONOS-A or CHRONOS-B.
- Up to 20 healthcare professionals who are responsible for recruitment across a geographical spread of sites.

- Trial monitoring visits to include trial coordinators' observations of participant recruitment to check for consistency of presentation across sites (e.g. at highest and lowest recruiting sites).

Patients will be sampled purposively to represent each group as described above. Demographic information will be collected and reported descriptively but not used as sampling criteria. Consecutive participants approached for the study and consecutive participants consenting to the study will continue to be recruited until the numbers designated above have been interviewed across the sites to ensure homogeneous groups. Sample groups may be of mixed age and ethnicity. If differences affecting the experiences of particular participants, e.g. by age or ethnicity, become apparent during data collection, further sample groups will be allocated.

Patients who decline to consent to the trial will be interviewed to explore their understanding of the trial processes and reasons for non-consent. Information gathered from non-consenter interviews will be fed back to the TMG to inform future trial recruitment strategies. Additionally, relevant positive or negative feedback from ongoing trial participants will be reported.

Further, the patients' experience will be impacted by physician equipoise, and the quality of consultation, therefore through interviews and recordings we aim to optimise the provision of clear and balanced information for patients about treatment options and possible participation in CHRONOS.

5.5.3 Timing of interviews

Interviews will take place as soon as possible after consultation about the trial or soon as possible after randomisation to capture immediate understanding and perceptions of trial processes. The feasibility of embedding longitudinal patient reported experience in the main trial will be assessed by serial interviews with three participants every two to three months.

5.5.4. Qualitative Study Sites

Participants will be recruited from the pilot sites. Other sites (including PIC sites if enrolled) will be considered if recruitment is compromised by delayed site openings or otherwise.

5.5.5. Approaching Patients

As described above.

5.5.6. The Interviews

Patients will be able to choose between undergoing interviews in a quiet environment within their treating hospital, within a University setting, within their own home or over the telephone if more convenient. Interviews will be approximately 30-60 minutes in length and will be terminated earlier at the participant's discretion if they become fatigued or unwell. The researcher's safety will be monitored by standard operating procedures for safe home visiting.

The qualitative researcher will use their experience to gauge topic saturation and completion of data sets. Topics covered in the interviews, in line with the aims above, will include;

- Practical management of the treatment interventions in everyday life.
- Managing the treatment regimes.
- Treatment impact on function, health and wellbeing.

- Personal needs and expectations of treatments.
- Perceptions of the trial and potential improvements.

Interviews will be digitally audio-recorded. Recordings will be managed in line with GCP and GDPR; participants will be fully informed about the use of their data and will be able to fully withdraw from the qualitative dataset, if requested. Confidentiality and safe storage of interview data will be standardised using a standard operating procedure. Recordings will be transcribed in full, verbatim, and anonymised to support the analysis process.

5.5.7. Analysis

Anonymised transcripts will be analysed using deductive thematic analysis techniques, with a coding framework developed to reflect the trial outcomes. Analysis will begin with two qualitative researchers individually coding the first three interview transcripts. The researchers will work closely together to agree a coding structure for the remaining interview transcripts towards the development of an analysis framework. The data sets will be coded in full and organised into themes and subthemes. The analysis framework will be refined as transcription, validation and assessment of categories and themes continues, until all transcripts have been coded. This data will be presented in a narrative format and interpreted within the context of patient experience to inform outcomes and reflect the aims of the trial.

5.5.8 Confidentiality and data storage

Information regarding study participants will be kept confidential and managed in accordance with the GDPR, NHS Caldicott Guardian, the UK policy framework for Health and Social Care, and Research Ethics Approval. Qualitative data and participant identifying details will be stored at Cardiff University and stored separately from recordings, transcripts and data analysis notes. Where real time participant data is used, the study team will ensure patients' clinicians are not privy to the data at any time, thus ensuring patient confidentiality. If clinicians are present during meetings where findings are shared, they will be blinded to this section of the meeting, by being asked to leave the room. A laptop may be used to store data temporarily when conducting field-work, but any data will be transferred securely using an encrypted USB stick to a Cardiff University PC and information held on the laptop and USB stick will be deleted. This will be recorded in data management records stored within the study site file. The laptop will be password protected and all files and documents pertaining to the study will also be password protected.

All hard-copy data and study information will be kept secured in locked filing cabinets within Cardiff University. All electronic data will be kept securely on a password protected computer and files and folders will also be password protected. Electronic files will be held on a University secured server. Only qualitative research staff will have access to the secure drive.

Digital audio recordings of interviews will be uploaded to the secure drive at Cardiff University and the originals deleted from the digital recorder. Audio recordings will be kept in a separate folder to any transcripts. Once transcribed and checked, interview transcripts will be stored in PDF format on the secured drive, which will ensure content cannot be altered. All transcripts will have identifiable information removed and replaced with pseudonyms Transcripts will be prepared in house (Cardiff University) by an experienced transcription secretary following a standard operating procedure for quality assurance, or by a university approved transcription service. Transcripts will be uploaded to the NVivo 11 qualitative software programme for efficient and rigorous data management. Participants will be asked to consent to the use of anonymised extracts in the study report and publications, education and conferences.

Participants will be asked for consent to share anonymised data, or for secondary analysis of the data as a separate consent item, and with a separate box to be initialled. All voice data will be deleted at the end of the study. Anonymised transcripts will be stored securely for 10 years. No data will be transferred outside the EU. Any future publications related to the study will ensure participant responses are anonymised.

5.5.9 Participant Identifiable Information

Patient identifiable data will comprise names and contact details. These will be known to the study qualitative researcher, the site research nurse and the patient's care team (as copies of the participant information sheet and consent form will be placed in the medical notes). Transcripts will be anonymised before data analysis by qualitative researchers. Only the transcriber and qualitative researcher will be aware of associated names and pseudonyms. This information will be held in accordance with the confidentiality statement above. An administration file will be kept securely at Cardiff University containing all participant contact details alongside the signed consent forms. A second data collection file will also be kept which will contain all anonymised data collected including interview transcripts. These two files will be kept separately. Both files will be available only to the qualitative researcher. The files will be stored in separate locked cupboards at Cardiff University in a passcode restricted building/ floor.

5.5.10. Safety Reporting (Interviews)

It has been deemed unlikely by the study team that participants may be adversely affected by taking part in the interviews. However, it is possible that as a result of taking part in the interviews participants may experience distress regarding their condition and the effect it has on their lives. To ensure the study team become aware of this, participants will be provided with a contact card, which contains the contact details of the qualitative researcher to report any issues arising from taking part in the interview. Any such contact made will be recorded on the adverse event form and reported to the CHRONOS Trial Manager, relevant R&D department and ethics committee (if deemed appropriate). Participants will also be directed to hospital based and independent support agencies as per local practice.

5.5.11. Presentation of Results

Real time data will be used throughout the duration of the study. Final results will be triangulated with other study data towards the end of the study and prepared for submission as part of the end of study report.

5.6 Integrated Health Economic Analyses

The aim of the economic analysis nested alongside the main trial uses the NHS perspective to determine the cost per QALYs (CUA), cost per PFS/FFS (CEA) and cost and consequences (CCA) to inform the decision regarding which arm is most appropriate. Data on resource-use, FFS and quality-of-life (as measured by EQ-5D-5L) collected alongside the trial are used for the analysis. CRFs validated in the pilot study will be used to collect patient NHS resource usage. Alongside CUA and CEA we also propose the use of cost and consequences analysis to account for any important aspect of care that might emerge from the qualitative analysis and not captured via EQ-5D-5L or PFS/FFS (e.g. burden of treatment routine). A series of one-way, multi-way and probabilistic sensitivity analyses will be carried out to test the robustness of results.

Alongside CUA and CEA we also propose the use of cost and consequences analysis to account for any important aspect of care that might emerge from the qualitative analysis and not captured via EQ-5D-5L or PFS/FFS (e.g. burden of treatment routine). A series of one-way, multi-way and probabilistic sensitivity analyses will be carried out to test the robustness of results.

5.7 Visit Schedule

The design and number of visits mirror the standard of care pathway for patients undergoing either focal therapy or radical therapy, so that additional patient burden is minimal. Prior to enrolment, all patients will have undergone a Prostate Specific Antigen (PSA) blood test, a diagnostic prostate MRI and prostate biopsies. A standard of care (SOC) multi-disciplinary team case review will precede any discussion with the patient on all suitable treatment options and trial suitability. After an MDT discussion confirming suitability for FT and/or radical therapy has taken place, a patient information sheet (PIS) explaining the study will be provided, after which patients will be given a minimum of 24 hours to consider taking part. We aim for consent to be taken during a SOC appointment, or an additional consultation via phone, or in person. Randomisation will take place during the visit in which consent is taken along with any required neoadjuvant therapy, as allocated via randomisation, to be prescribed and within 24 hours of receiving the prescription. Time from randomisation will be used to define progression free survival and failure free survival. The end of treatment is defined as the final part of any intervention. For radiotherapy, this is the final radiation fraction completed and for prostatectomy and focal therapy the point at which the catheter is removed. Therefore, the follow-up visits noted below will start from these time-points, which will define the date of first follow-up visit (visit 2).

Visit Schedule:

	Screening & Consent	Visit						
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	6 monthly visits until last visit 60 months after visit 2
Months			**These below specify the months *after* the completion of each treatment in each arm**					
		0	**3**	**12**	**18**	**24**	**30**	31-60. Visits 4 onwards can be telephone consultations in order to note clinical outcomes although MRI scans and biopsies where done will require physical visits to the hospital
Informed Consent and enrolment into either CHRONOS A or CHRONOS B	X							
Inclusion & exclusion criteria checked, including concomitant medication review	X							
Randomisation	X							
Prescription of neo-adjuvant therapy	X (if randomised to such arm)							Within 24hrs of randomisation
PSA blood test			X	X	X	X	X	X (6 monthly)
Prostate Contrast MRI	X (if randomised to focal therapy and no contrast given during diagnostic scan – to have prior to visit 2)							
Prostate mpMRI				X (focal therapy arms)				
Biopsy (optional)				X (focal therapy arms)				
Treatment		X (these vary in length)						X (focal therapy arms – a second treatment will be permitted for a histologically confirmed recurrent, residual or new out-of-field disease)
Clinical assessment (optional, only if required)			X	X	X	X	X	
PROMS questionnaires	X		X	X		X		X (every 12 months, at 24, 36, 48 and 60 months visits)
Review/ reporting of patient AEs/SAEs		X	X	X	X	X	X	X
Blood and urine tests including those for	X		X	X				X

biobanking (optional)								

Time window for each visit will be +/- 4 weeks

5.8 Treatment

CHRONOS-A

- Arm 1 (Control arm): Radical therapy (prostatectomy or radiotherapy [external beam or brachytherapy]). The type of radical therapy will be determined by physician or patient preference.
    - In radiotherapy patients, neoadjuvant ADT permitted and if given, minimum 3 months and maximum 6 months duration.
    - We anticipate lymph node treatment in this group is not required but 'for cause lymph node treatment will be permissible if strong clinical preference is demonstrated.
    - If an extended lymph node dissection is anticipated this will need to be discussed in a central review by the surgery subgroup.
    - As per Radiotherapy Trials Quality Assurance (RTTQA) centres and physicians delivering radiotherapy will need to be approved.
    - Radiotherapy detailed protocols will be set out in a separate SOP.
    - Surgeons and surgical centres currently are approved as a national commissioning programme so any centre or surgeon permitted to carry out radical prostatectomy in standard NHS practice will be permitted to deliver prostatectomy within this trial.
    - Prostatectomy details will be set out in a separate SOP.

- Arm 2 (Intervention arm): Focal therapy alone (high intensity focused ultrasound [HIFU] or cryotherapy or other validated energy modality as per physician/patient decision/choice. Other energy modality will only be added after TSC and TMG approval and a substantial amendment approved by all required bodies.
    - A second treatment either in-field or out-of-field will be permitted either after the MRI and optional biopsy showing clinically significant cancer at 12-months or due to suspicion of residual or new contralateral disease at a future date with a positive biopsy for clinically significant cancer.
    - Cryotherapy can be used after HIFU and HIFU can be used after cryotherapy. This second focal therapy session will be part of the focal therapy intervention
    - Where patients have undergone hemiablation to one lobe and then undergo hemiablation of the contralateral lobe will be designated as failure of focal therapy
    - Focal therapy details will be set out in a separate SOP.

Patients previously or currently on 5 alpha reductase inhibitors or anti-androgens, or LHRH agonists or LHRH antagonists are still eligible for CHRONOS A.

CHRONOS-B

- Arm 1 (Control arm): Focal therapy alone (high intensity focused ultrasound [HIFU] or cryotherapy or other validated energy modality 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. Cryotherapy can be used after HIFU and HIFU can be used after

cryotherapy. Where patients have undergone hemiablation to one lobe and then undergo hemiablation of the contralateral lobe will be designated as failure of focal therapy

- Arm 2 (Intervention arm): Neoadjuvant finasteride 5mg once daily for a minimum of 12 weeks (84 days) followed by focal therapy (as per control arm).
- Arm 3 (Intervention arm): Neoadjuvant bicalutamide 50mg once daily therapy for 12 weeks (84 days) followed by focal therapy (as per control arm).

Other arms can be added in future with protocol amendments.

5.9 Follow-up

Follow-up will consist of serum Prostate Specific Antigen (PSA) tests at 3 months and 12 months after completion of treatment as defined above. Thereafter, PSA will be measured 6-monthly until a progression event is determined, for 5 years after initial randomisation or mortality (whichever is first).

Patient reported outcome measures (PROMs) will be collected at 3 and 12 months and then annually thereafter until progression, mortality or 5 years after initial randomisation (whichever is first). The minimum follow-up for each patient will be 5 years in the main study although yearly follow-up will continue long term in clinical standard care through linkage to national databases.

NB: if the trial does not proceed to the Main Stage following the analysis of the Pilot, patients will be followed up for a minimum of 3 months and will then revert to standard of care in which the clinical care provided to patients will not differ from the clinical follow-up stipulated in this protocol. At the end of the study patients will continue to be followed up locally within their recruitment centres within the ICE (European Registry for Cryosurgical Ablation of the prostate, EuCAP) or the HEAT international HIFU registry as per NICE guidelines IPG432/IPG42.

Patient reported outcome measures

The EORTC QLQ-C30 with the prostate-specific module, International Prostatic Symptoms Score (IPSS), EPIC bowel and bladder and International Index of Erectile Function 15 (IIEF15) will be used.

The EuroQol (EQ-5D) will be used in the study as a generic measure of health-related quality-of-life which can be linked to public preferences. These data will be used to calculate quality-adjusted life-years as part of a future health economic evaluation. Patients agreeing to return questionnaires on quality of life should continue to complete quality of life data for 5 years after randomisation. Questionnaires should be self-administered, although it is recommended that a key person (e.g. research nurse) at each centre be responsible for the data collection to optimise compliance and completeness of the data.

The patients should complete the quality of life and the resource use data questionnaires independently without discussion with friends or relatives and all questions should be answered. The member of the study team should check each questionnaire and query any missing or incorrect data with the patient. Checks should also take place for date and identifiers. Patients should be approached at appropriate visits to complete the questionnaires.

Follow-up consultations

Collection of data at each 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. In certain circumstances it may be appropriate to replace hospital visits with telephone or email consultations providing that it is still possible to collect all the necessary follow-up information. In order to maintain confidentiality during email consultations these episodes will be conducted via the local site practitioner's protected NHS email account. Such remote consultations are undertaken frequently in routine clinical care and in these instances, it is acceptable to perform appointments with telephone or email consultations providing the required blood results, such as PSA tests are available to the research team (can be performed at local hospital or GP practice as per patients request and the GP's discretion). In any instance the hospital will carry out these tests if the GP was to refuse. All necessary information required to complete the follow-up case report form (CRF) is still required. All details on the telehealth consultations must be recorded in the patients' notes.

Study Visits - specific tests and definitions of failure

Focal therapy

- A prostate mpMRI and an optional targeted transrectal or transperineal prostate biopsy of the treated area at 12 months after focal therapy in CHRONOS-A and CHRONOS-B. Biopsies of the untreated area should only occur if new areas of score 4 or 5 occur. Those men who did not have a diagnostic quality mpMRI compliant with national guidelines before focal therapy should have biopsies of treated and untreated areas, if this is done. A biopsy SOP will give detail the requirements of the biopsy.
- As there is no defined time-point for a PSA nadir value following FT the PSA value at 12-months post randomisation in patients with a negative MRI 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, instrumentation/procedures, biopsies, catheterisation), a for-cause mpMRI with or without biopsies can be carried out at the discretion of the treating clinician. The Focal Therapy Sub-Group should be informed of this and a review of the for-cause mpMRI findings prior to biopsy should be carried out. Clinically significant prostate cancer in-field that is suitable for further FT should be offered to patients as a routine. Radical therapy should be only recommended to patients in instances where further FT is not suitable. Such situations should only occur after the Focal Therapy Sub-group has reviewed the case as expertise for such decisions may not reside in the local centre.
- In CHRONOS A, a second treatment either in-field or out-of-field will not be classified as failure and is part of the overall focal therapy intervention. In patients who undergo a second treatment of FT the nadir value will be defined at the 12-month time point after the second treatment, provided mpMRI and biopsy targeted at treated area(s) are negative for clinically significant prostate cancer.

<u>Radiotherapy/ Brachytherapy</u>

- In 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. Staging scans should be done as

per local practice. Where salvage local or systemic therapy is given, this will be regarded as PFS event.

Surgery

- Adjuvant or salvage radiotherapy will be regarded as a PFS event and will be determined based on histological findings and PSA kinetics even if the biochemical failure definition is not reached (PSA >/=0.2ng/ml). Staging scans should be done as per local practice.

- Biochemical failure following radical therapy as internationally defined, even if salvage therapy is not given, will be counted as an event for PFS/FFS analyses.

Collection of postcodes
In order to get an area-based estimate of deprivation, the participants' postcodes will be converted into an Index of Multiple Deprivation (IMD) score. The IMD is the established index of deprivation for England Wales and has been adopted widely in studies across local and national government. Postcodes will not be stored in the InForm Database only IMD rank, which is based on detailed ward-level index of deprivation based on severe separate domains.

Prostate Specific Antigen (PSA)
Blood sample for PSA can be collected during a scheduled hospital visit or at a hospital local to the patient or at a community/primary care facility, whichever is more convenient for the patient provided the result is available to the research team.

Patient reported outcome measures (PROMS)
PROMS questionnaires can be completed or returned during a scheduled hospital visit or via post/electronic communication.

Further follow-up imaging
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.

Further follow-up biopsies
Some patients will undergo further biopsies if there is a need to confirm disease progression after the 12 month follow-up visit following focal therapy.

Further interventions
Some patients will also undergo secondary non-cancer related procedures to manage adverse events from the therapy such as, but not limited to, transurethral resection of prostate, bladder neck incision, urethral dilatation, optical urethrotomy, male-sling or other continence procedures as well as penile implant surgery for impotence. Endoscopic tests or interventions of the lower bowel may also be required. These rates of interventions will be collected.

Future follow-up
Patients will be consented for their names to be linked to national registries for survival information such as NHS Information Centre/Office of National Statistics (ONS) in England/Wales and General Register Office in Scotland, Hospital Episode Statistics (HES).

Biochemical Failure
For the purposes of this trial, biochemical failure will be defined after surgery and radiotherapy/ brachytherapy as per standard care. Early adjuvant or salvage therapy can be given prior to biochemical failure if clinically determined through an MDT. These will count as events for purposes of PFS. Focal therapy does not have a validated definition for biochemical failure.

- Radiotherapy/ brachytherapy: PSA nadir plus 2ng/ml as per Phoenix definition
- Surgery PSA >/=0.2ng/ml at any time-point after surgery

Confirming biochemical failure

The timing and thus assessment of PSA needs to be considered because rises in PSA can occur due to non-cancer related causes such as after procedures, biopsies or urinary tract infection (UTIs). Confirmatory samples are needed in all cases of a rising PSA prior to assigning an outcome of biochemical failure. After biochemical failure is confirmed for the first time it need not be reported again.

In the case that the raised PSA value reaches the biochemical failure value, a second confirmatory PSA test should be performed after at least 1 week or after 4 weeks after the completion of treatment in cases of UTIs, procedures or biopsies. Biochemical failure is confirmed if the second value also confirms this. The date of biochemical failure should be provided as the date of the **first PSA** that fulfilled the definition for failure.

If salvage treatment does start before the trial definition of biochemical failure is met then report the closest PSA value prior to the treatment start date as the progression value.

5.10 Laboratory Evaluations

Blood test: PSA will be measured as per standard care and using local laboratory processes and assays. Centralised measure of PSA will not be used. No additional haematology or biochemistry tests will be mandated by the trial. It is envisaged that standard of care haematological and biochemical tests will be ordered by the treating clinician to monitor for pre-assessment requirements for anaesthetic fitness or for assessing treatment related toxicity.

Urinalysis: No additional urinalysis test will be mandated by the trial.

Exploratory / Research samples: Research samples including tissue, blood and urine will be collected and stored as per the details below and will be taken at each of the predefined time points. Protocols for analysis will be added as substantial amendments. Patients will be informed that exploratory studies will take place and consent will be taken for these at initial recruitment. The exact nature of these studies will not be disclosed and further consent in the future will not be asked for prior to proceeding. The following statements have been added to the PIS:

"*All samples taken will be transferred to the Imperial College Healthcare Tissue Bank or partner biobank in the UK and will be used for histological, genomic and epigenetic analysis and for ethically approved future studies by our team or other scientists interested in prostate cancer research. Samples will not have any personal information written on them. Researchers will not be able to identify you from your samples.*"

The following statement has been added to the Informed Consent Form:

"*I give permission for any blood, urine and tissue samples, as described in the information sheet, to be used for this and for further ethically approved research in the field of prostate cancer research. I give permission for my samples and data from any scans to be sent and be utilised in research both in the UK and worldwide. All material will be anonymous and I will not be identifiable. I understand that I will not be asked again for permission to run these additional research tests and I may also not be informed of the results.*"

Sample storage and analysis

All additional research samples that are taken will be processed, handled and stored at the Imperial College Health Care Tissue Bank (ICHTB) or partner UK biobank as per their standard operating procedures (SOPs). Transfer of biobanked samples may be needed to local, national and international laboratories and this will be in accordance with the ICHTB or our partner laboratory SOPs both within and outside of the UK.

The standard care urine samples taken as part of routine clinical care will be stored for 7 days post analysis and then auto disposed in tiger stripe (offensive waste) bag as per the Trust Clinical Waste Management Policy.

Urine samples may be collected and stored for biobanking and may in future undergo further analysis if new biomarkers are discovered that may be of clinical use in diagnosing prostate cancer (optional consent). Urine samples for biobanking will be stored in -80' C freezers within approved biobank facilities at Imperial College Healthcare Tissue Bank or a partner UK biobank for a period of 10 years.

Blood for standard care tests in clinical care will be via peripheral venepuncture and placed in a plastic tube containing SST (serum separating tube). This will be processed in a local laboratory. The blood samples will be stored for 4 days post analysis and then auto disposed to bio-bins and incinerated off site according to the Trust Clinical Waste Management Policy.

Additional blood samples may be collected and stored for biobanking and in future may undergo further analysis if new biomarkers are discovered that may be of clinical use in diagnosing prostate cancer (optional consent). Blood samples for biobanking will be stored in -80' C freezers within approved biobank facilities at Imperial College Healthcare Tissue Bank or partner UK biobank for a period of 10 years. At the end of the study if there are any samples left these will be held under the Imperial College Healthcare Tissue Bank (ICHTB) HTA licence 12275 and any further use of the samples will be approved via an ethics approval committee within the ICHTB.

Blood and urine samples taken for biomarkers will be collected at the local treating hospital site and transferred to the aforementioned biobank facilities for storage.

Samples may also be transported for tests that can only be run outside of the UK. If needed ethics approval will be sought for any such tests.

Imaging scan data

Imaging scans are performed as part of this study. We will also ask for optional consent from patients to store and use their scan data in future research to see if new ways of looking at these scans 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. We will ask patients if they are happy to give consent for their health status to be followed up over time. This will be done by linking 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 and 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.

6. TREATMENTS

6.1 Investigational Medicinal Product (IMP) Details

Neoadjuvant finasteride and bicalutamide are used within standard practice. However, they are considered investigational medicinal products within CHRONOS as they are being used to discover, verify and compare their clinical effects with focal therapy.

CHRONOS-B (only)

- Arm 2 (Intervention arm): **Neoadjuvant finasteride** 5mg once daily for a minimum of 12 weeks (84 days) followed by focal therapy.
- Arm 3 (Intervention arm): **Neoadjuvant bicalutamide** 50mg once daily therapy for a minimum of 12 weeks (84 days) followed by focal therapy.

6.2 Labelling and Packaging

Neoadjuvant finasteride and bicalutamide are open label and will be dispensed from the site local pharmacy stock according to normal pharmacy protocol. Any brand/ formulary of finasteride and bicalutamide are permissible within CHRONOS B.

6.3 Storage and Dispensing

Neoadjuvant finasteride and bicalutamide will be stored and dispensed according to normal pharmacy protocols. Patients should store their medication as indicated in the Summary of Product Characteristics (SmPC) leaflet which is included in the standard packaging.

6.4 Dosage, Duration and Compliance

Patients randomised to CHRONOS-B Arm 2
- Neoadjuvant finasteride 5mg once daily for 12 weeks (84 days) therapy followed by focal therapy. The medication will be prescribed and dispensed within 24 hours of randomisation.

Patients randomised to CHRONOS-B Arm 3
- Neoadjuvant bicalutamide 50mg once daily for 12 weeks (84 days) followed by focal therapy. The medication will be prescribed and dispensed within 24 hours of randomisation.

As part of compliance assessment, patients will be asked to return their blister packs after the 12 week treatment duration is complete. Ideally, they should provide them to the local research team at the subsequent focal therapy visit. Compliance will also be reported regularly in the CRF.

6.5 Accountability

The returned blister packs should be kept in a safe location at the local site, with the Patient Identifier number clearly marked on the packaging and the paper and electronic CRF accountability logs completed. Returned blister packs must be accessible to the Study Monitor for accountability assessment during monitoring visits.

6.6 Drug Interactions/ Precautions/ Contraindications

Finasteride
Interactions:
No drug interactions of clinical importance have been identified.

Precautions:
Obstructive uropathy
Advised for patients to use effective contraception during treatment due to risk of morphological changes in spermatozoa

Contraindications:
Hypersensitivity reaction to 5-alpha reductase inhibitors

Bicalutamide
Interactions:
Severe: none identified
Moderate: Lomitapide*
Mild: none identified
*theoretical

Precautions:
Risk of photosensitivity- advised to avoid exposure to UV light and sunlight
Monitoring of liver function tests required- accumulation may occur in moderate to severe hepatic impairment

Advised for patients to use effective contraception during treatment due to risk of morphological changes in spermatozoa
No dose adjustment is required in the elderly patients or patients with renal impairment

Contraindications:
Hypersensitivity to anti-androgen therapy

6.7 Overdose of IMP

Finasteride
There is no known antidote and therefore symptomatic and supportive treatment should be given.
Bicalutamide
There is no known antidote and therefore symptomatic and supportive treatment should be given.

6.8 Dose Modification for Toxicity

Finasteride
No dose changes are recommended for renal or hepatic impairment
Bicalutamide
No dose changes are recommended for renal impairment
Advised caution in patients with moderate- severe hepatic impairment

6.9 IMP Drug Administration

Patients will self-administer neoadjuvant finasteride and bicalutamide by mouth. The local research physician/nurse will explain the treatment frequency and duration to the patient.

6.10 Non-Investigational Medicinal Product (Non-IMP) Details

Standard of care treatments will be prescribed as per their approved use. The study will not mandate type or dosage of any standard of care medication or treatment for treatment of prostate cancer. Physicians will be asked to declare which they will use upfront prior to randomisation and for this to be documented in the trial CRF.

6.11 Permanent Discontinuation of Study Treatment and Withdrawal from Study

i. Permanent discontinuation of study treatment
Subjects may discontinue study treatment for the following reasons:
- At the request of the subject.
- Allergic reaction to IMP
- If the investigator considers that a subject's health will be compromised due to adverse events or concomitant illness that develops after entering the study.

ii. Withdrawal from Study
Withdrawal from the study refers to discontinuation of study treatment and study procedures and can occur for the following reasons:
- Subject decision
- Loss to follow-up

iii. Procedures for Withdrawal from Study

Every effort should be made to follow-up all patients who have been randomised. Patients should, if possible, remain under the care of an oncologist or urologist for the duration of the trial. If care of a patient is returned to the GP, it is the responsibility of the responsible clinician who obtained the patient's consent to participate in the trial to ensure that all relevant data collection forms are completed. Nurse-led follow-up is permitted and should be conducted in line with local practice and procedures.

If the patient moves away from the local area, arrangements should be made for trial follow-up to be undertaken by their new local centre. Details of other participating centres can be obtained from the Study Manager. If the responsible clinician moves, appropriate arrangements should be made to arrange for trial follow-up to continue at the centre.

All efforts should be made to preserve the patient's initial consent for long-term survival information to be flagged through national registries, for example NHS Digital (previously the Health and Social Care Information Centre); Office of National Statistics (ONS) in England/Wales; General Register Office in Scotland; Hospital Episode Statistics (HES) or Public Health England.

In order to do this we will provide all patients an optional consent to provide identifiable information for us to trace the patient on the National Health Service Care Register (NHSCR) for an additional 10 years.

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 on their health status and quality of life. This will allow us to track what happens after the study finishes to observe if anyone gets cancer in future and about the type of cancer and the treatment they have had. Results of the optional health status check will also help us to refer to any future upcoming studies.

7. PHARMACOVIGILANCE/ ADVERSE EVENT REPORTING

The Common Terminology Criteria for Adverse Events (CTCAEv4.0) will be used to report adverse events. Please refer to for further details:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

7.1 Adverse Event (AE)

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

i. Adverse Event recording

For the purposes of the study, AEs will be followed up according to local practice until the event has stabilised or resolved, or the Follow-up Visit, whichever is the sooner. All SAEs will be recorded throughout the study and should be reported to the sponsor and any unexpected

and related SAES should also be reported to the REC (as per attached JRCO SOP – appendix 3).

ii. Severity of Adverse Events

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

iii. Causality of Adverse Events

- *Unrelated:* No evidence of any causal relationship

- *Unlikely:* There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after trial interventions). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
- *Possible:* There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial interventions). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

- *Probable:* There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

- *Definite:* There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

7.2 Abnormal Laboratory Test Results

All clinically important abnormal laboratory test results (apart from PSA) occurring in patients assigned to Arms 2 and 3 in CHRONOS-B will be recorded as adverse events. The clinically important laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the clinical monitor, or until a diagnosis that explains them is made.

7.3 Serious Adverse Events (SAE)

i. Definition of SAE

An SAE is defined as any event that:

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

* "Life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

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

List of expected adverse events that may require hospitalisation and serious adverse events that will not require reporting as SAEs but will be collected:

- Urinary retention and any admission required for this
- Urinary tract infection and any admission required for this
- Epididymo-orchitis and any admission required for this
- Dysuria
- Debris in urine and any admission required for this
- Haematuria and any admission required for this
- Erectile dysfunction and any other sexual sequelae side-effects such as dry orgasm, lack of orgasm, poor libido
- Urinary incontinence
- Rectal discomfort, bleeding, diarrhoea
- Recto-urethral fistula and any operations required for this
- Lethargy, tiredness, poor appetite
- Urethral stricture and any operations required for this
- Transurethral resection of prostate and any operations required for this
- Operations required for symptoms of bladder outlet obstruction
- Any expected complication related to post-operative course from radical prostatectomy i.e. lymphocoele, bowel injury, haematoma needing percutaneous drainage
- Expected toxicity from systemic therapy such as neutropenia, neutropenic sepsis, weight gain, decreased libido, breast tenderness, metabolic syndrome, lethargy, fatigue, osteoporosis, nausea and vomiting, diarrhoea, constipation, muscle/joint pains and hair loss.
- Bowel stricture post radiotherapy, and procedures required for this

ii. Reporting of SAEs

Rapid reporting of all SAEs i.e. within 24 hours, occurring during the study must be performed as detailed in SAE reporting instructions. If the investigator becomes aware of safety information that appears to be intervention related, involving a subject who participated in the study, even after an individual subject has completed the study, this should be reported to the Sponsor.

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

Reporting of SAEs and review by the CI will be via the trial data collection system (CRF/electronic case report form [InForm]).

iii. Related SAEs

Related: results from administration of any research procedures

iv. Unexpected SAEs

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

v. Reporting of SAEs that are related and unexpected

Please Note: These reporting requirements refer to CHRONOS-A only

An SAE form should be completed on the InForm eCRF within 24 hours. However, relapse, death and/or hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All related and unexpected SAEs should be reported to the relevant REC as per the following definition. In the opinion of the Chief Investigator, the event was:

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

Contact details of sponsor for reporting SAEs are as follows:

Joint Research Compliance Office:
Imperial College London and Imperial College Healthcare NHS Trust
E-mail: jrco.ctimp.team@imperial.ac.uk

Chief Investigator:
Professor Hashim Uddin Ahmed
Imperial College London, Charing Cross Campus
E-mail: hashim.ahmed@imperial.ac.uk and chronos@imperial.ac.uk
Tel: 020 7589 5111 (Mon to Fri 09.00 –17.00)

vi. Definition of a Serious Adverse Reaction (SAR)

Please Note: This definition refers to CHRONOS-B only

A SAR is defined as a SAE that is judged to be related to any dose of study drug administered to the subject.

For the purpose of this study, reactions would apply to the combined administration of neoadjuvant therapies with focal therapy:
- Neoadjuvant finasteride followed by focal therapy
- Neoadjuvant bicalutamide followed by focal therapy

vii. Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

Please Note: This definition refers to CHRONOS-B only

Any SAR that is NOT consistent with the applicable product information as set out in the Summary of Product Characteristics (SmPC).

viii. Reporting of SUSARS

Please Note: These reporting requirements refer to CHRONOS-B only

SUSARS should be notified to the appropriate regulatory authority, the relevant REC and the Sponsor in accordance with regulatory requirements. SUSARs which are fatal or life-threatening will be reported no later than seven days after alerting the Sponsor to the reaction. Any additional relevant information will be sent within eight days of the report. A SUSAR which is not fatal or life-threatening will be reported within 15 days. Follow-up of patients who have experienced a SUSAR should continue until recovery is complete or the condition has stabilised.

7.4 Annual Progress Reports

Annual Progress Reports will be submitted to the Research Ethics Committee, the Regulatory Authority and the Sponsor in accordance with local requirements. The Annual Progress Reports will detail all SAEs recorded.

7.5 Pregnancy

Not application as the study population is male.

7.6 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken and give written notice to the MHRA, the relevant research ethics committee (REC) as well as the sponsors of the measures taken and the circumstances giving rise to those measures. The sponsor in any case should also be informed of urgent safety measures.

8. STATISTICAL ANALYSES

8.1 Sample Size and power considerations

8.1.1 Feasibility and Pilot Stage

For both CHRONOS-A and CHRONOS-B feasibility is considered in terms of recruitment rate, the acceptability of the trial randomisation and adherence to arm allocation.

- CHRONOS-A: A two-arm RCT will recruit 1190 patients over a total recruitment and follow-up period of 8 years. The number and nature of centres involved would require between 1-2 patients recruited per-centre per-month. At a conservative rate, we expect to recruit 60 patients in the Pilot Stage in 6 centres over 12-months.

- CHRONOS-B: A three-arm* MAMS RCT 1260 patients to be recruited over five years at a rate of 20 patients per month. The number and nature of centres involved would require between 1-2 patients recruited per-centre per-month. Conservatively, we expect to recruit 60 patients in the Pilot Stage in 6 centres over 12-months.

*Further arms may be added via substantial amendments

N.B. Patients observed in the Pilot Stage will be included in the Main Stage. In the event that the study does not proceed from Pilot to Main, patients recruited into the Pilot will be followed up for 6 months for safety monitoring.

8.1.2 Main study

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. The question is what margin of non-inferiority should be in the main study. In the CHHIP radiotherapy RCT a 20% relative change was acceptable as a non-inferiority margin comparing one form of radiotherapy to another form of radiotherapy HR 1.208; absolute difference 5%). 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.

For a patients' perspective, we can look at the unpublished NCRN COMPARE study (presented at NCRI UK Annual Conference, November 2018). This was a discrete choice experiment where 544 newly diagnosed men (~30 UK centres) were asked to make choices between different treatment scenarios. Marginal Rate of Substitution (MRS) were calculated (trade-offs men are willing to make between side-effects and survival). On average men are willing to trade 0.68% of survival chance against 1% chance of improving urinary function, with PFS and sexual function MRS at 0.41% and 0.28%. Based on the above, 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 is based on an assumption 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).

Table 1. Sample size calculations

	Stage 1	Stage 2	Overall
Alpha	0.45	0.025	0.044
Power	95%	85%	83%
Critical HR (guidance for stopping early)	0.974		-
Control Arm Events	47	120	-
Accrual	20pts/m	20pts/m	20pts/m
Cumulative Patients	1003	1200	-
Time to analysis (years)	3.4	4.2	7.6

8.2 Planned recruitment rate

Within the UK approximately 10,000 patients meeting our eligibility criteria undergo radical therapy a year and 700 patients undergo FT. Thus, the potential pool of eligible patients is large and the timeline to full accrual is based on UK estimates and would allow both CHRONOS-A and CHRONOS-B to complete recruitment within 5 years and primary outcome analysis to occur after 8 years. For the pilot stage 120 patients (60 each for CHRONOS-A and CHRONOS-B) will be recruited from approximately 6 sites over 12-months. The pilot will assess feasibility of our recruitment timelines and final recruitment rates will be based on the data from the pilot.

The recruitment rate will be assessed as part of our pilot and timelines for the main stage will be adjusted accordingly. In order to allow the majority of UK sites to be eligible for the study, we will develop a centralised process for the delivery of trial therapies/interventions. In brief, if a site does not have direct access to either FT or radiotherapy or surgery then there will be a process in place for the treatment to take place in a nearby trial site that offers that treatment.

8.3 Statistical analysis

Feasibility and pilot study

The primary analysis of the feasibility stage will estimate recruitment and randomisation rate to allocated arm. Safety in terms of Adverse Events will be analysed in terms of occurrence of adverse events in each arm.

The main study will be initiated if the minimum target recruitment rate of the feasibility study is within the lower end of the confidence interval and funding has been confirmed.

Main study

Time-to-event (progression or failure depending on which of CHRONOS-A or CHRONOS-B) data will be presented using Kaplan-Meier plots. In all time-to-event analyses, patients that have not experienced the event in question will be censored at the date last seen/known to be alive. The hazard ratio (HR) will be taken from a Cox proportional hazards model, adjusted for any stratification factors used at randomisation. Differences in time-to-event outcomes will be assessed using the log-rank c2 test and expressed using a hazard ratio (HR) with a 2-sided 95% confidence interval. If there is evidence of non-PH in the treatment

effect, the HRs are difficult to interpret and the restricted mean survival time (RMST) constructed from a flexible parametric model with time varying treatment effects will take primacy.

The assumption of proportional-hazards (PH) will be tested and appropriate methods applied to the data in the case of any violation. If there is no evidence of non-PH in the treatment effect, the HR for the adjusted Cox model takes primacy. If there is evidence of non-proportional hazards in the treatment effect, the HRs are difficult to interpret and the restricted mean survival time constructed from a flexible parametric model with time varying treatment effects will take primacy.

Planned interim and sub-group analyses: Each research comparison will have a pilot stage, one pre-planned interim analysis on PFS or FFS if the research comparison were to continue to a main stage study, and a final efficacy stage on PFS or FFS.

Planned interim analyses for education: there will be a review of recruitment into each research arm and these results as well as the qualitative outcomes will be used for submission for a research doctoral thesis of Deepika Reddy supervised by the Chief Investigator of this trial. The thesis will be embargoed to public release as deemed necessary by the TSC/DMC**.**

CHRONOS-B: Interim monitoring and analyses: For each research comparison one formal intermediate analysis is planned, where an activity “hurdle” is determined on the intermediate primary outcome measure, FFS. Each research arm needs to pass this in order to continue recruitment. This will initially be timed according to the observed number of interim events required for a formal interim analysis (Table 2).

Table 2: Guidelines for stopping accrual and trigger for analysis

Stage	Arm Ratio	Target HR	One-sided alpha	Power	HR cut-point	Control arm events
2 Activity	1:1	0.67	0.45	95%	>0.974	~47FFS
3 Efficacy	1:1	0.67	0.025	85%	-	~120FFS
Overall	-	-	0.044	83%	-	-

For each comparison that continues recruitment into its final efficacy stage, the final analysis will be triggered by a pre-specified number of definitive primary outcome events being reported for the relevant patients on the control arm of that comparison (Table 2).

Further details of the planned analysis of the secondary outcomes and methods for dealing with missing data will be given in the Statistical Analysis Plan. Any deviation from the statistical analysis plan will be described and the reason for the deviation explained.

i. Primary Outcome Measure Analysis

The primary endpoint (PFS or FFS) analysis consists of a Cox proportional hazard model to investigate the effect of the intervention on PFS/FFS adjusted by the stratification variables.

The assumption of proportional-hazards (PH) will be tested and appropriate methods applied to the data in the case of any violation. If there is no evidence of non-PH in the treatment effect, the HR for the adjusted Cox model takes primacy. If there is evidence of non-proportional hazards in the treatment effect, the HRs are difficult to interpret and the

restricted mean survival time (RMST) constructed from a flexible parametric model with time varying treatment effects will take primacy.

ii. Secondary Outcome Measure Analysis

Details of the secondary endpoints analysis will be outlined in the Statistical Analysis Plan document, which will be written and signed off before any analysis will commence.

iii. Adjusted analysis

Analysis will be adjusted by the pre-specified stratification variables

iv. Safety Analysis

Safety analysis consists in tabulating the frequency of serious adverse events.

9. REGULATORY, ETHICAL AND LEGAL ISSUES

9.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the 7th revision of the 1964 Declaration of Helsinki.

9.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 (R2) guidelines).

9.3 CTA

This study has Clinical Trials Authorisation from the UK Competent Authority; MHRA. Reference: CTA 19174/0409/001-0001

9.4 Independent Ethics Committee Approval

i. Initial Approval

Prior to the enrolment of subjects, the Research Ethics Committee (REC) and Medicines and Healthcare products Regulatory Agency (MHRA) must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Patient Information Sheet and Consent Form, any other written information that will be provided to the subjects, any advertisements that will be used and details of any subject compensation.

ii. Approval of Amendments

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

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

iii. Annual Progress Reports

The REC will be sent annual progress reports in accordance with national requirements.

iv. Annual Safety Reports and End of Trial Notification

The REC will be sent annual safety updates in order to facilitate their continuing review of the study (reference. ICH GCP E6 (R2) Section 3.1.4) and will also be informed about the end of the trial, within the required timelines. The Annual Progress Report will detail all SAEs recorded.

9.4 Regulatory Authority Approval

The study will be performed in compliance with UK regulatory requirements. Clinical Trial Authorisation from the appropriate Regulatory Authorities must be sought/obtained as applicable to local country regulations prior to the start of the study, if appropriate. In addition, the Regulatory Authorities must approve amendments prior to their implementation (as instructed by the Sponsor), receive SUSAR reports and annual safety updates, and be notified of the end of the trial.

9.5 HRA approval

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

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

9.6 Other Required Approvals

The Chief Investigator will ensure that the procedures are compliant with the Ionising Radiation (Medical Exposure) Regulations, and appropriate review by a Medical Physics Expert and Clinical Radiation Expert has been undertaken.

9.7 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF (InForm) and reviewed by the Chief Investigator and reported to the ICTU QA Manager on a monthly basis. Protocol violations will be reported to the Sponsor.

An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.

A serious breach is defined as:

A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the UK trial subjects; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the MHRA and REC within 7 days of becoming aware of the serious breach.

9.8 Insurance and Indemnity and Sponsor

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

9.9 Trial Registration

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

9.10 Informed Consent

Subjects will be provided with a copy of the signed Subject Information Sheet/Informed Consent Form document. The original Informed Consent Form should be retained with the source documents.

9.11 Contact with General Practitioner

It is the investigator's responsibility to inform the subject's General Practitioner (where applicable) by letter that the subject is taking part in the study provided the subject agrees to this, and information to this effect is included in the Subject Information Sheet and Informed Consent. A copy of the letter should be filed in the medical notes.

9.12 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the CRF or other documents submitted to the Sponsors, subjects will be identified by a subject ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to subjects' records and source documents for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS and regulatory authorities.

9.13 Data Protection and Patient Confidentiality

The investigator will preserve the confidentiality of all participants taking part in the study, which will be conducted in accordance with GDPR and the Data Protection Act. Furthermore, all investigators and study staff must comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

9.14 End of Trial

The end of the trial will occur at the point of database lock or at the request of the Trial Steering Committee.

9.15 Study Documentation and Data Storage

The study investigators and study site staff will comply with the requirements of the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

The investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Subject files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents

should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

All research documentation and information will undergo a process of pseudonymisation where possible. Whilst within the study, patients will be identified by a unique study number, and the data in the CRF will be linked to this number. Research data will be entered onto a dedicated, secure, encrypted trial database, specifically constructed for this purpose. The study team will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer. Data within the NHS system such as patient notes, and reports will remain confidential in accordance with NHS confidentiality code of practice.

Paper enrolment logs, including patients' names, NHS numbers and dates of birth, will be kept in the Investigator Site File and will be stored in a secure, locked room. Electronic documents will be kept on secure and encrypted computers. Access to these documents will be highly restricted and will only be available to the relevant research team members.

No study documents will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

10. DATA MANAGEMENT

10.1 Source Data

Source documentation is defined as the first time data appear, and may include original document, data and records (hospital records, clinical reports, MRI and Ultrasound reports, other procedure reports, laboratory notes, other data recorded at the pathology and biochemistry laboratories, etc.). Information in source documents (e.g. medical history) dated prior to the Informed Consent Form signature date may be used to verify patient suitability for the study.

Clinical records must be marked to indicate a subject has been enrolled into the clinical study.

The Investigator must ensure the availability of source documents from which the information on the eCRF was obtained. Where printouts and electronic medical records are provided as source documents, they should be signed and dated by a member of the adequately trained research team, to indicate that the data provided is a true reproduction of the original source document.

All study data may be inspected by the Sponsor and regulatory authorities by people working on behalf of the Sponsor, and by representatives of Regulatory Authorities, where it is relevant to this research.

10.2 Language

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

10.3 Database

The principal means of data collection from participant visits will be Electronic Data Capture (EDC) via the internet using the InForm database and the REDCap database which will be used to collect follow up data. Data is entered into the EDC system via site personnel. All source data will be recorded in the CRF and the completed case report book will be signed by the Investigator or his/her appropriate designee. All changes made at any time following the electronic signing will have an electronic audit trail with a signature and date. The completed case report book will then again be signed by the investigator or his/her appropriate designee. Specific instructions and further details will be outlined in the CRF manual. At the end of the study patients undergoing focal therapy will continue to be followed up locally within their recruitment centres within the ICE (European Registry for Cryosurgical Ablation of the prostate, EuCAP) or the HEAT international HIFU registry as per NICE guidelines IPG432/IPG42.

10.4 Data Collection

All study data will be entered into electronic Case Report (eCRFs) in a database provided by the Sponsor (InForm/REDCap). All eCRFs will be completed using de-identified data.

CRF completion may be delegated by the Principal Investigator (documented on the Delegated Task List) to other study personnel though the Principal Investigator remains responsible for the accuracy and integrity of all data entered to eCRFs.
Further details of procedures for CRF/eCRF completion, including data review, database cleaning, issuing and resolving data queries, and identification of steps for creation, modification, maintenance and archiving of source data via any computerised systems will be provided in the study specific Data Management Plan (CRF manual). At the end of the study patients undergoing focal therapy will continue to be followed up locally within their recruitment centres within the ICE (European Registry for Cryosurgical Ablation of the prostate, EuCAP) or the HEAT international HIFU registry as per NICE guidelines IPG432/IPG42.

10.5 Archiving

All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 10 years following the end of the study. Subject files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved later. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act 2018 (UK).

11. STUDY MANAGEMENT STRUCTURE

11.1 Trial Steering Committee

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

is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

11.2 Trial Management Group

A Trial Management Group (TMG) will be convened including the Chief Investigator (co-chair), lead co-investigator (co-chair) and other co-investigators and key collaborators, Study Statistician and Study Manager. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate Terms of Reference. When necessary, decisions will be referred to the TSC. Meetings will be scheduled in a risk-adapted manner to allow for the review of events during the trial.

11.3 Data Monitoring Committee (DMC)

A combined Data Monitoring and Trial Steering Committee will meet twice per year basis. The composition of this committee will include but not be limited to an Independent Chair, Independent Statistician, and Independent Clinician. The Study Team, Trials Unit representatives, and Patient representative will attend by invitation of the committee.

11.4 Early Discontinuation of the Study

In case of early discontinuation of the study, the Follow-up Visit assessments should be performed for each subject, as far as possible.

The following reasons may result in early discontinuation:

- Early evidence that a treatment arm is harmful. If only one treatment arm is deemed to be harmful then the remaining arms of the study may continue as planned, OR
- It is not feasible to reach the planned outcomes (A hazard ratio of 0.7 to 1 will make the intervention not worth progressing with given the severe adverse effects associated with it)

The statistical criteria for termination of the study will be detailed in the statistical analysis plan (SAP). At the end of the study patients undergoing focal therapy will continue to be followed up locally within their recruitment centres within the ICE (European Registry for Cryosurgical Ablation of the prostate, EuCAP) or the HEAT international HIFU registry as per NICE guidelines IPG432/IPG42.

11.5 Risk Assessment

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

11.6 Monitoring

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 (R2) guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

Monitoring procedures and requirements will be documented in a Monitoring Plan, developed in accordance with the risk assessment.

11.7 Quality Control and Quality Assurance

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

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

11.8 Peer review

This study has been peer reviewed by funder Prostate Cancer UK and within the Urology Department at Imperial College London. It has also undergone review by the NCRI (UK) Prostate Clinical Studies Group.

11.9 Patient and Public Involvement

We recognise the value of patient involvement and have already included patient perspectives at all stages.

Chris Dobbs is an experienced patient representative that we have worked with in other prostate cancer trials. He has been involved from the outset in defining the research question and guiding us to relevant patient outcomes; he was a co-applicant to the grant and will be a member of the Trial Management Group. He is a member of the PCUK Grants Advisory Panel. Areas in which his input has been sought or will be sought are:

- Design of the research
- Management of the research
- Undertaking the research
- Analysis of results
- Dissemination of findings

In developing this proposal, we ran a patient focus group in Oct-2016 of 8 men both with and without recurrence after focal therapy on rationale, eligibility criteria, follow-up strategies, and outcomes. There was unanimous agreement on the rationale and men rated quality of life as a primary consideration. Men were willing to have neoadjuvant strategies provided the side-effect profile was low. From the discussed options (hormonal therapy, immunotherapy, low-dose chemotherapy, metformin), we decided on 2 initial neoadjuvant strategies for this proposal. The men accepted a medium-term outcome of local failure. They would have been willing to undergo randomisation for this study.

11.10 Publication and Dissemination policy

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

It is understood by the investigator that the Sponsor will use information developed in this clinical study in connection with the development of the ablative or radiotherapy or surgical techniques and, therefore, may disclose it as required to other clinical investigators and to Regulatory Authorities. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore, all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) is completed.

Permission from the Executive/Writing Committee is necessary prior to disclosing any information relative to this study outside of the Trial Steering Committee. Any request by site investigators or other collaborators to access the study dataset must be formally reviewed by the TMG.

The results may be published or presented by the investigator(s), but the Funder will be given the opportunity to review and comment on any such results for up to 1 month before any presentations or publications are produced.

A Clinical Study Report summarising the study results will be prepared and submitted to the REC and MHRA within a year of the end of study. The results will also be submitted to the EudraCT results database in accordance with regulatory requirements.

12. REFERENCES

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SIGNATURE PAGE 1 (Chief Investigator)

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Comparative Health Research Outcomes of NOvel Surgery in prostate cancer

Protocol Number: 19CX5006

Signed: _____

Professor Hashim U Ahmed

Date: _____

Lead Co-Investigator

Signed: _____

Mr Taimur Shah

Date: _____

SIGNATURE PAGE 2 (Sponsor)

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

Study Title: Comparative Health Research Outcomes of NOvel Surgery in prostate cancer

Protocol Number: 19CX5006

Signed: _____

Name of Sponsor's Representative
Title
Sponsor name

Date: _____

SIGNATURE PAGE 3 (Statistician)

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

Study Title: Comparative Health Research Outcomes of NOvel Surgery in prostate cancer

Protocol Number: 19CX5006

Signed: _____

Dr Francesca Fiorentino
Imperial Clinical Trials Unit and Division of Surgery

Date: _____

SIGNATURE PAGE 4 (Principal Investigator)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Comparative Health Research Outcomes of NOvel Surgery in prostate cancer

Protocol Number: 19CX5006

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____