Statistical Analysis Plan (SAP): Feasibility v1.0 10MAR21

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

IP4 - CHRONOS

19CX5006

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Contents

1. 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

2. Background and Rationale

2.1. 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 recognized, 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). Further to the described side effects, radical therapies have an approximate failure rate of 10-15% at 5-years following treatment (2) (3) (4) (5) (6) (7).

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. Advances in imaging 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 (9).

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 (10).

2.2. Rationale for CHRONOS

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 (antiandrogen) 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.

3. Study Objectives

3.1. CHRONOS-A

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

3.2. CHRONOS-B

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.

4. CHRONOS-A and CHRONOS-B Internal 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 end points 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 optimise 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-NAHA 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.

5. CHRONOS-A and CHRONOS-B Pilot Outcome Measures

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 proportions of participants completing study interventions and follow-up imaging and biopsy. The reasons for withdrawal will be documented with a questionnaire given to individuals.

This study includes an integrated qualitative component which will be conducted and analysed by the team at the University of Cardiff, and so is not included in the SAP. 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.

5.1. Primary Outcome Measures

Feasibility of recruitment, acceptance of randomisation and compliance to allocated arm.

- Recruitment is defined as total number of patients recruited (consented) out of the total number of patients approached.
- Randomisation is defined as the total number of patients randomised out of the total number of patients recruited (consented).
- Compliance comprises of treatment compliance (CHRONOS-A and CHRONOS-B) and drug compliance (CHRONOS-B):
    - Treatment compliance (CHRONOS-A and CHRONOS-B):
        - Proportion of patients who underwent treatment (Focal therapy ((CHRONOS-A and CHRONOS-B)), Radiotherapy/Brachytherapy or Prostatectomy (CHRONOS-A)) as recorded by date of treatment and completed treatment details recorded at Visit 2/3 (treatment visit)
    - Drug compliance (CHRONOS-B). This will be measured in two ways:
        - Proportion of patients who returned their empty blister pack (yes/no), as recorded at Visit 3.
        - Proportion of patients who were given the drug (recorded at Visit 2) and who did not have a registered protocol deviation (stating that the drug was taken for less than 8 weeks).

5.2. Secondary Outcome Measures

- Patients' experience of consent and recruitment, including reasons for declining participation[1].
- Patients' motivation to accept randomisation to, and compliance with an intervention and understanding of each trial arm[1].
- 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[1].
- Potential improvements to recruitment processes[1].
- To establish the feasibility of an economic evaluation alongside the main trial[1].

[1]These outcome measures are to be analysed as part of the embedded qualitative study conducted by the team at the University of Cardiff. These will not be included in the SAP.

6. Design

6.1. Study Design

CHRONOS will be performed in the UK. This is a randomised, unblinded multicentre study, including two 1:1 parallel randomised controlled trials targeting the same patient population. The comparator is standard of care. The two linked RCTs (CHRONOS-A and CHRONOS-B) will be discussed with patients and the choice of A or B will be dependent on physician and patient equipoise.

6.1.1. CHRONOS-A

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

6.1.2. CHRONOS-B

Focal therapy will be delivered to all patients, and subjects will be further randomised to receive neoadjuvant and/or adjuvant therapy using a MAMS design.

We plan to consider a number of neoadjuvant and/or adjuvant strategies that make mechanistic sense, such as hormonal therapy or immune-modulation. The MAMS design is adaptive, allowing comparison of multiple research arms with a common control arm and incorporating the pilot and effectiveness stages. 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. 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 two-arm RCTs. A smaller overall number of patients are needed, fewer resources are used and research questions are answered in a timely fashion.

6.2. Treatment Groups

6.2.1. 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 control 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
- Focal therapy details will be set out in a separate SOP.

6.2.2. 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.
- 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, as part of the main trial, with protocol amendments.

6.2.3. Summary of Treatment Groups

Treatment Sequence	Number of subjects	Details
CHRONOS-A		
Control arm	Pilot: 30	Radical radiotherapy or radical prostatectomy (as per physician and patient decision/preference
Intervention arm	Pilot: 30	Focal therapy using HIFU or cryotherapy (as per physician and patient decision/preference)
Total number	Pilot: 60	
CHRONOS-B		
Control arm	Pilot: 20	Focal therapy using HIFU or cryotherapy (as per physician and patient decision/preference)
Intervention arm 1	Pilot: 20	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	Bicalutamide 50mg once daily for 12 weeks followed by focal therapy (as per standard care control arm for CHRONOS-B)
Total number	Pilot: 60	

6.3. Study Population

Men with non-metastatic prostate cancer who are suitable for focal therapy and radical therapy will be approached for recruitment into CHRONOS (CHRONOS-A and CHRONOS-B offered simultaneously).

6.4. Eligibility Criteria

6.4.1. Inclusion Criteria

- PSA ≤ 20 ng/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 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 is met:
    - The index lesion to be treated if focal therapy is used meets the above histological criteria.
    - The patient may have a PIRADS of 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.
- No restriction exists in CHRONOS-A on previous or current use of 5-alpha reductase inhibitors or anti-androgens or LHRH agonists or LHRH antagonists.
- 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.

6.4.2. 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.

6.5. Blinding

This is an open label RCT.

6.6. Sample Size

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.

6.6.1. 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.

6.6.2. 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.

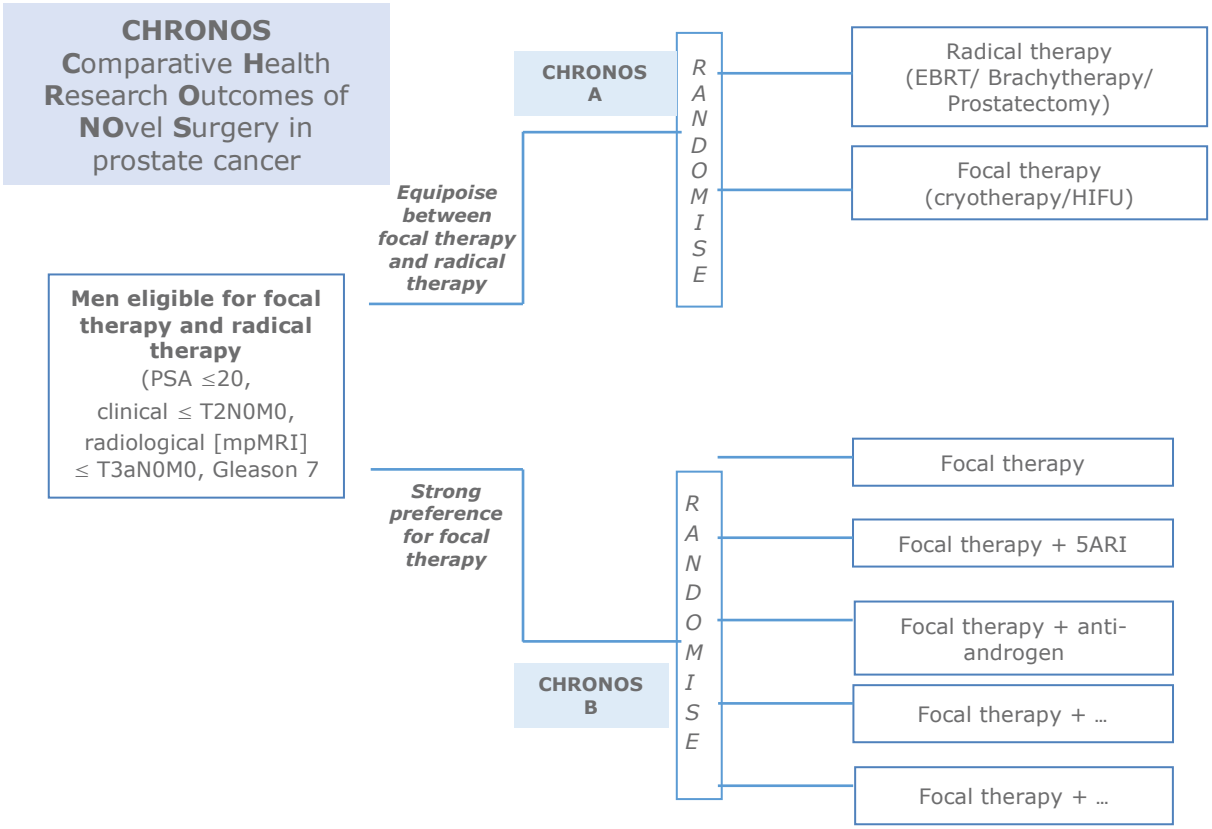
*Further arms may be added, to the main trial, via substantial amendments

N.B. Patients observed in the Pilot Stage will be included in the Main Stage. In the event that the study does not proceed 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 the study protocol.

We will consider adjusting the sample size for the main stage to incorporate the compliance and feasibility results from the analysis described in Section 9.

6.7. Schedule of Time and Events

6.7.1. Study Flow Chart



6.7.2. 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).

	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				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)

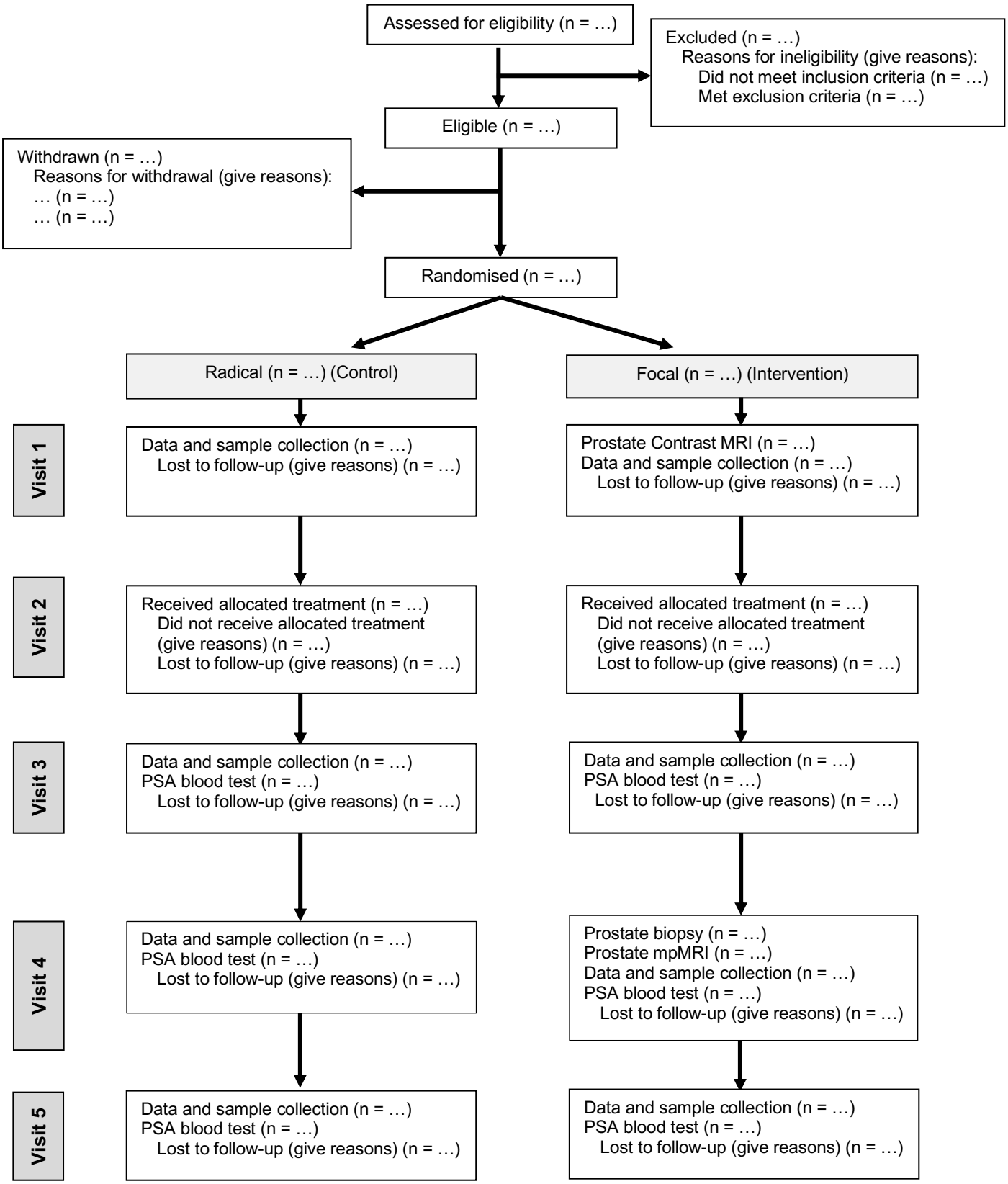
Review/ reporting of patient AEs/SAEs		X	X	X	X	X	X	X
Blood and urine tests including those for biobanking (optional)	X		X	X				X

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

Minimum length of follow up for the pilot will be 3 months from treatment for each patient. Then treatment will revert to standard of care.

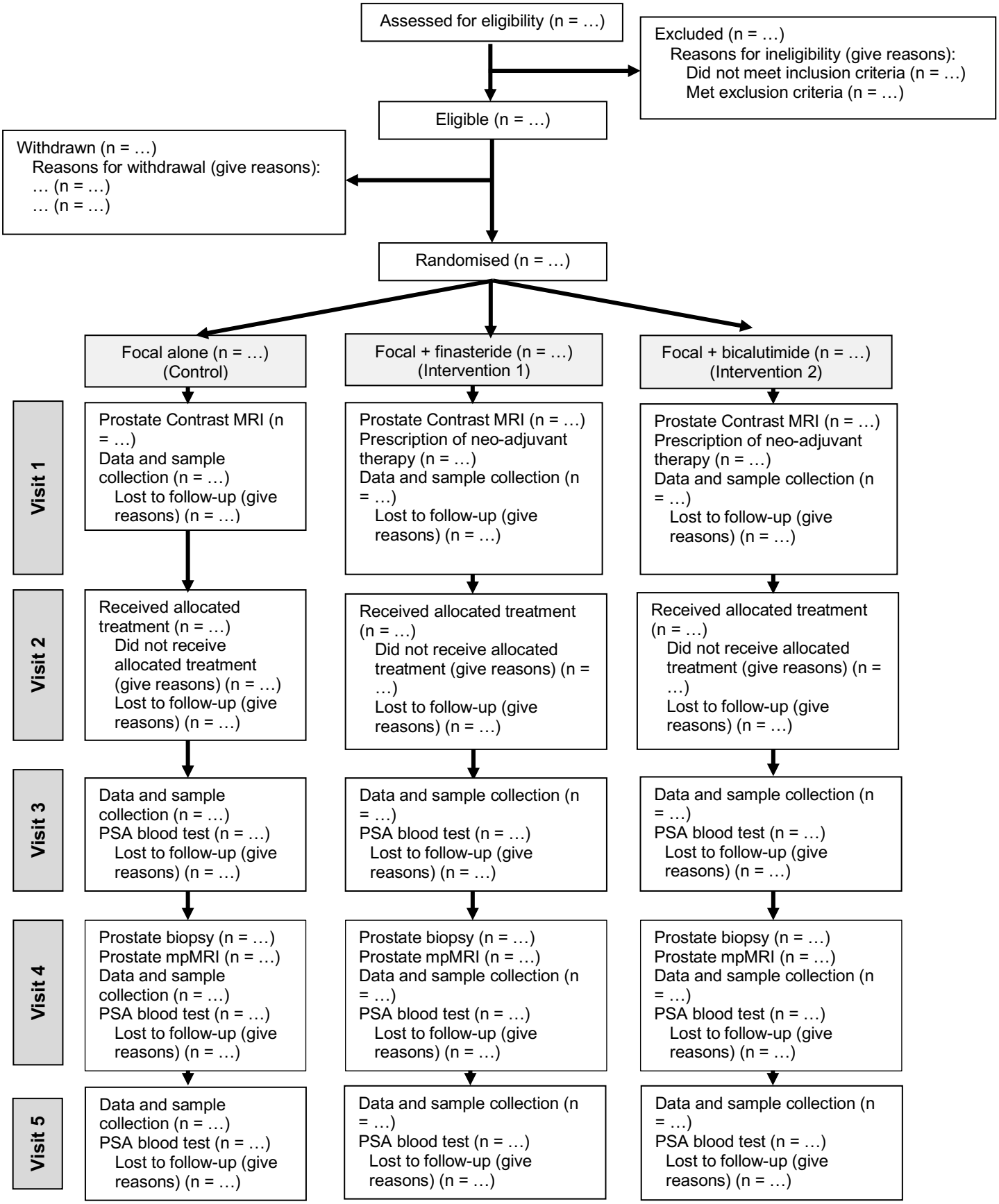
6.7.3. Internal Pilot: CONSORT Diagram

6.7.3.1. CHRONOS-A[1]



[1]CONSORT diagram could be extended to include more visits dependent on the data collected for the pilot

6.7.3.2. CHRONOS-B[1]



[1]CONSORT diagram could be extended to include more visits dependent on the data collected for the pilot

6.8. 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 5-alpha reductase inhibitor use.

7. Analysis Set

All objectives will be analysed using all patients approached for enrolment in the trial, and randomised patients according to the intention to treat principle.

8. Variables of Analysis

8.1. Baseline Demographic Variables

After obtaining informed consent and registering the patient in one of the studies (CHRONOS-A or CHRONOS-B), the following clinical and baseline assessments will be undertaken:

- Demographics: age, ethnicity, IMD decile
- Digital Rectal Examination results
- Details of current medications
- IPSS score
- MCCL and Gleason grade at pre-enrolment biopsy.

8.2. Safety Variables

An adverse event (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.

A serious adverse event (SAE) is defined as any event that:

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's 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 admission that were planned before study inclusion or visits to casualty (without admission).

AE reporting will utilise NCI CTCAE v4.0 terminology, providing a grading (severity) scale for each AE term. The expected adverse events that may require hospitalisation and serious adverse events that will not require reporting as SAEs, but that will be collected, are listed in **Error! Reference source not found.**.

All protocol deviations and violations will be recorded throughout the study and reported.

8.3. Primary End Point Variables

- Numbers of men approached for CHRONOS-A and CHRONOS-B per month per centre

- Numbers of men recruited to CHRONOS-A and CHRONOS-B per month per centre
- Numbers of men randomised to CHRONOS-A and CHRONOS-B per month per centre
- Total number of men completing each stage for each treatment arm of CHRONOS-A and CHRONOS-B
- Number of days between consent and randomisation in days:
    - Date of consent
    - Date of randomisation
- Number of days between randomisation and start of treatment (CHRONOS-A and CHRONOS-B):
    - Date of randomisation
    - Date of focal therapy (CHRONOS-A (Focal arm) and CHRONOS-B)
    - Date of treatment visit (CHRONOS-A (Radical arm))
- Treatment form information and date of visit (collected at Visit 2) (CHRONOS-A and CHRONOS-B)
- Focal therapy information (collected at Visit 2) (Focal arm of CHRONOS-A and CHRONOS-B):
    - Date of Focal Therapy
    - Form of Focal therapy performed
    - Focal therapy ablation schema
    - Seminal vesicle treatment
- Radiotherapy/Prostatectomy information (collected at Visit 2) (Radical therapy arm of CHRONOS-A):
    - Radiotherapy/Brachytherapy Log (CHRONOS-A (Radical therapy)):
        - Form of radiation treatment undergone
        - Radiotherapy treatment details (which radiotherapy regime was performed, whether the patient had lymph node radiotherapy, whether patient completed their radiotherapy course)
        - Brachytherapy treatment details (whether the patient underwent treatment as planned, whether the patient underwent radiotherapy boost alongside brachytherapy, confirmed on post-procedure dosimetry).
    - Prostatectomy Log (CHRONOS-A (Radical therapy)):
        - Whether the patient underwent radical prostatectomy or not.
- Neoadjuvant drug information (collected at Visit 2) (CHRONOS-B):
    - Date neoadjuvant treatment was commenced
    - Whether empty blister pack has been returned
    - Date empty blister pack was returned
    - Registered protocol deviations for drug compliance
        - Registered protocol deviations which state that the drug was taken for less than 8 weeks
- Number of days between consecutive visits:
    - Date of visit
- Number of days between randomisation and start of neoadjuvant drug treatment (CHRONOS-B):
    - Date of randomisation
    - Date neoadjuvant drug treatment commenced (CHRONOS-B)
- Number of days between start of neoadjuvant drug treatment and start of focal therapy (CHRONOS-B)
- Occurrence of adverse events not listed in Appendix 1 (see Section).

8.4. Secondary End Point Variables

- EQ-5D-5L: five dimensions and EQ VAS (see Appendix 2 for more details)
- IIEF15: 15 questions (see Appendix 2 for more details)
- EPIC-26: 26 questions (see Appendix 2 for more details)
- EPIC – URINARY FUNCTION: 7 questions (see Appendix 2 for more details).

9. Statistical Methodology

9.1. Baseline Demographics

Summaries will be presented for CHRONOS-A and CHRONOS-B separately. Patient characteristics will be summarised by treatment arm. Summaries of continuous variables will be presented as means and standard deviations if approximately normally distributed, and as medians and inter-quartile ranges for skewed data; categorical variables will be presented as frequencies and percentages.

9.2. End Point Analysis Summary

End Points	Variables	Analysis	Population
Primary			

Feasibility and acceptance of randomisation (rate per-month per-centre averaged) and compliance to allocated arm	Recorded data on whether patients have been (CONSORT):
	• Recruited
	• Enrolled and consented
	• Randomised
	• Withdrawn/Lost to follow-up
	• In follow-up (and what stage of follow-up)
	• Completed
	
	• Days between consent and randomisation
	• Days between randomisation and start of treatment
	• Days between consecutive visits
	• Days between randomisation and start of neoadjuvant drug treatment (CHRONOS-B)
	• Days between start of neoadjuvant drug treatment and start of
		• Proportions of patients recruited to CHRONOS-A and CHRONOS-B
		
		• Mean number of patients recruited per month per centre
		• Recruitment rate
		• Graph displaying recruitment rate over time
		• Graph of actual vs target recruitment rate over time
		
		• Mean number of patients randomised per month per centre
		• Randomisation rate
		• Graph displaying randomisation rate over time
		
		• CONSORT diagram, including:
		  • Reasons for ineligibility
		  • Number who attended each visit in each arm
		  • Number of patients who received their allocated treatment/intervention
		
		• Summary statistics for time between consent and randomisation by treatment arm
		• Summary statistics for time between randomisation and treatment by treatment arm
		• Summary statistics for time between consecutive visits
		• Summary statistics for time between randomisation and start of neoadjuvant drug treatment (CHRONOS-B only)
		• Summary statistics for time between start of neoadjuvant drug treatment and start of focal therapy(CHRONOS-B only)
			All patients approached for enrolment and all patients randomised

	focal therapy (CHRONOS-B) • Treatment details (as recorded at Visit 2/3) • Protocol deviations for treatment compliance • Reasons for ineligibility • Reasons for withdrawal	• Treatment compliance: o Proportions of patients who underwent their allocated treatment (as recorded at Visit 2/3) • Drug compliance (CHRONOS-B only): o Proportions of patients who returned their empty blister pack (yes/no) (as recorded at Visit 3) o Proportions of patients who were given the drug and do not have a registered protocol deviation stating that they took the drug for less than 8 weeks • Reasons for ineligibility • Reasons for withdrawal • Kaplan-Meier plots of time to withdrawal from randomisation • Baseline characteristics for those who withdrew and those who completed each trial	
	Safety analysis: AE and SAE data	• Summarise AE data by treatment arm and by site • Summarise SAE data by treatment arm and by site	All patients randomised
Secondary			
Patients' experience of each arm including systemic issues, erectile dysfunction, urinary symptoms and rectal symptoms	• EQ-5D-5L • IIEF15 • EPIC-26	Summarise each questionnaire by time point and by treatment arm **<u>EQ-5D-5L:</u>** • Health profiles for each treatment arm at each desired time point – proportions by dimension and level • Histograms of frequency • EQ VAS – summary statistics for each treatment arm at each time point • Histograms of frequency **<u>IIEF15 / EPIC-26 / EPIC-URINARY DOMAIN:</u>** Summary statistics for each domain, for each time point by treatment arm	All patients randomised

	• EPIC-URINARY DOMAIN		

All analyses will be repeated for CHRONOS-A and CHRONOS-B separately.

9.3. Primary End Point Analysis

The proportions of patients who opted for CHRONOS-A and CHRONOS-B will be reported.

The primary analysis of the internal pilot will calculate the mean number of patients recruited and randomised per month, per centre (including only the months in which the centre is open and recruiting). Overall recruitment and randomisation rates will also be calculated, along with their corresponding 95% confidence intervals. Recruitment rate is calculated as the number of participants recruited out of the total number approached. Randomisation rate is calculated as the number of participants randomised out of the total number recruited. Graphs displaying the recruitment and randomisation rates over time will be presented. A graph displaying the actual vs target recruitment rates will also be presented. These analyses will be conducted for CHRONOS-A and CHRONOS-B.

Compliance will be summarised using the CONSORT diagram for the internal pilot (see Section 1.1.1) which includes, the number of men who have withdrawn or been lost to follow-up (with reasons), and the number who completed each stage within each treatment arm. There will be a separate CONSORT for CHRONOS-A and CHRONOS-B.

Summary statistics for time between consent and randomisation, and randomisation and treatment will be presented by treatment arm. Summary statistics will also be presented for time between consecutive visits, by treatment arm.

For CHRONOS-B only, summary statistics will also be presented for time between randomisation and start of neoadjuvant treatment, and time between start of neoadjuvant treatment and start of focal therapy.

Treatment, for CHRONOS-A and CHRONOS-B, is recorded at Visit 2 (Treatment Visit). For focal therapy arms (CHRONOS-A (Focal arm) and CHRONOS-B) treatment is recorded by date of treatment and completed treatment details at Visit 2. For the radical arm of CHRONOS-A, treatment is recorded by date of visit 2 and completed treatment details on Radiotherapy/Brachytherapy Log and Prostatectomy Log at Visit 2. The proportions of patients in each treatment arm who underwent treatment will be presented, along with their corresponding 95% confidence intervals.

Treatment compliance will be evaluated by arm and by trial (CHRONOS-A/CHRONOS-B). Viable treatment compliance is defined as the lower end of the confidence interval for the proportion of patients who underwent treatment being $\geq$ 80%. If the lower end of the confidence interval for the proportion of patients who underwent treatment is $\geq$ 80%, then we have viable compliance to progress to the main phase. If the lower end of the confidence interval for the proportion of patients who underwent treatment is between 70% and 80%, then this indicates that remedial work is needed to improve this for the main stage. If the lower end of the confidence interval for the proportion of patients who underwent treatment is < 70%, then this could affect the primary outcome analysis and threaten the validity of the study. Data will be presented to the TSC for a final decision in this case.

Neoadjuvant drug treatment in CHRONOS-B is prescribed at randomisation. Drug compliance will be estimated using two definitions:

- Patients who returned their empty blister packs (yes/no) at Visit 3
- Patients who took the drug and did not have a registered protocol deviation stating that they took the drug for less than 8 weeks.

For CHRONOS-B only, the proportions of patients who returned their empty blister packs (yes/no), and the proportions of patients who took the drug and did not have a registered protocol deviation, stating that they took the drug for less than 8 weeks, in each treatment arm will be reported, along with their corresponding 95% confidence intervals. Drug compliance will be evaluated by arm and by trial for each of the drug compliance definitions. Viable drug compliance is defined as the lower end of the confidence interval for the proportions being $\geq$ 90%. If the lower end of the confidence interval for the proportions is between 80% and 90%, then this indicates that remedial work is needed to improve this for the main stage. If the lower end of the confidence interval for the proportions is < 80%, then this could affect the primary outcome analysis and threaten the validity of the study, and may require sample size re-estimation. Data for both drug compliance definitions will be presented to the TSC for a final decision in this case.

The reasons for ineligibility and withdrawal will be collected and recorded for CHRONOS-A and CHRONOS-B separately. Kaplan-Meier plots will be presented to show time from randomisation to withdrawal for CHRONOS-A and CHRONOS-B separately. Baseline characteristics will be compared between those who completed the Internal Pilot phase of the study, and those who withdrew from the Internal Pilot phase of the study.

Throughout the trial, adverse events will be recorded using the designed eCRFs. Reported adverse events (AEs) and serious adverse events (SAEs) will be listed, and then summarised, by treatment arm, in terms of severity grade (using v4.0 CTCAE grading) and causal relationship to treatment, for CHRONOS-A and B separately. Expected adverse events which are not to be reported as SAEs are listed in Appendix 1.

9.4. Secondary End Point Analysis

PROMs are collected throughout the feasibility phase at screening and 3 months.

EQ-5D-5L has five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, each measured using five levels of response (see Appendix 2). Summary statistics, by treatment arm, will be presented for each of the dimensions and levels, at each time point. Histograms will also be produced to display the proportions in each level for each dimension.

EQ VAS is an additional question on the EQ-5D-5L (see Appendix 2). This will be summarised, by treatment arm, at each time point.

IIEF15 consists of five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction (see Appendix 2). Summary statistics, by treatment arm, will be presented for each domain, at each time point.

EPIC-26 consists of five domains: urinary incontinence, urinary irritative/obstructive, bowel, sexual, hormonal (see Appendix 2). The response scores will be standardised using the method described in appendix 2. Summary statistics, by treatment arm, will be presented for each domain, at each time point.

EPIC-URINARY DOMAIN consists of four subscales: function, bother, incontinence and irritative/obstructive (see Appendix 2). The response scores will be standardised using the method described in appendix 2. Summary statistics, by treatment arm, will be presented for each domain, at each time point.

9.5. Impact of the Covid-19 Pandemic

To assess the impact of the Covid-19 pandemic on the feasibility phase of the trial, we will assess the baseline demographics, recruitment rate, randomisation rate, reasons for ineligibility, and time between consent and randomisation to see if there exist important differences between the population recruited before the Covid-19 pandemic and the population recruited during/after the Covid-19 pandemic.

Time between randomisation and treatment, treatment compliance (CHRONOS-A and CHRONOS-B) and drug compliance (CHRONOS-B) will be assessed between the population who

underwent treatment before the Covid-19 pandemic and those who underwent treatment during/after the Covid-19 pandemic.

Time between consecutive visits will be assessed between the population who underwent their most recent consecutive visit before the Covid-19 pandemic and those who underwent their most recent consecutive visit during/after the Covid-19 pandemic. Similarly, proportions of patients with missing or delayed visits will be assessed between patients who underwent that visit before the Covid-19 pandemic and those who underwent that visit during/after the Covid-19 pandemic.

Reasons for withdrawal will be assessed between the population who withdrew before the Covid-19 pandemic and the population who withdrew during/after the Covid-19 pandemic.

Trial processes and conduct will also be assessed for important differences between these populations. This analysis is detailed further in Section **Error! Reference source not found.**.

9.6. Missing Data

A specific missing data mechanism is not required for the Internal Pilot phase of the study.

9.7. Outliers

No formal method will be used for handling outliers in the Internal Pilot phase of the study.

9.8. Safety Analysis

Safety analysis will consist of tabulating the frequency of serious adverse events, and is part of the primary outcome analysis detailed in Section 9.3.

9.9. Protocol Deviations

Protocol deviations, and violations, are to be listed and summarised, if necessary, by category and treatment arm.

9.10. Tables to present

9.10.1. Baseline Characteristics

Table 1. 1: Baseline Characteristics (CHRONOS-A)

Variable	Statistics	Focal	Radical	Total
Age	N	xxx	xxx	xxx
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)
	Missing from eCRF – n (%)	xx (xx%)	xx (xx%)	xx (xx%)
Ethnicity – n (%)	N	xxx	xxx	xxx
	White	xx (xx%)	xx (xx%)	xx (xx%)
	Mixed	xx (xx%)	xx (xx%)	xx (xx%)
	Asian	xx (xx%)	xx (xx%)	xx (xx%)
	Black	xx (xx%)	xx (xx%)	xx (xx%)
	Other	xx (xx%)	xx (xx%)	xx (xx%)
	Missing from eCRF	xx (xx%)	xx (xx%)	xx (xx%)
IMD Decile – n (%)	N	xxx	xxx	xxx
	1	xx (xx%)	xx (xx%)	xx (xx%)
	2	xx (xx%)	xx (xx%)	xx (xx%)
	3	xx (xx%)	xx (xx%)	xx (xx%)
	4	xx (xx%)	xx (xx%)	xx (xx%)
	5	xx (xx%)	xx (xx%)	xx (xx%)
	6	xx (xx%)	xx (xx%)	xx (xx%)
	7	xx (xx%)	xx (xx%)	xx (xx%)
	8	xx (xx%)	xx (xx%)	xx (xx%)
	9	xx (xx%)	xx (xx%)	xx (xx%)
	10	xx (xx%)	xx (xx%)	xx (xx%)
	Missing from eCRF	xx (xx%)	xx (xx%)	xx (xx%)
Digital Rectal Examination – n (%)	N	xxx	xxx	xxx
	Yes:	xx (xx%):	xx (xx%):	xx (xx%):
	Normal findings[1]	xx (xx%)	xx (xx%)	xx (xx%)
	Abnormal findings[1]	xx (xx%)	xx (xx%)	xx (xx%)
	No	xx (xx%)	xx (xx%)	xx (xx%)
	Missing from eCRF	xx (xx%)	xx (xx%)	xx (xx%)
Current medications – n (%)	N	xxx	xxx	xxx
	Yes	xx (xx%)	xx (xx%)	xx (xx%)
	No	xx (xx%)	xx (xx%)	xx (xx%)
	Missing from eCRF	xx (xx%)	xx (xx%)	xx (xx%)
5 alpha-reductase inhibitor[2] – n (%)	N	xxx	xxx	xxx
	Yes over (or equal to) 6 months ago	xx (xx%)	xx (xx%)	xx (xx%)
	Yes within 6 months	xx (xx%)	xx (xx%)	xx (xx%)
	No	xx (xx%)	xx (xx%)	xx (xx%)
	Missing from eCRF	xx (xx%)	xx (xx%)	xx (xx%)
Stratification Factors				
Tumour grade (n (%))	Gleason 3+3	xx (xx%)	xx (xx%)	xx (xx%)
	Gleason 3+4	xx (xx%)	xx (xx%)	xx (xx%)
	Gleason 4+3	xx (xx%)	xx (xx%)	xx (xx%)
Local stage (n (%))	Clinical T2/Radiological stage	xx (xx%)	xx (xx%)	xx (xx%)
	<T3a	xx (xx%)	xx (xx%)	xx (xx%)

	Radiological T3a			
Previous or current 5ARI use? (n (%))[3]	Yes No	xx (xx%) xx (xx%)	xx (xx%) xx (xx%)	xx (xx%) xx (xx%)

[1]Proporiton out of the total number of men who had a DRE

[2]Proportion out of the total number of men who are taking current medications

Table 1. 2: Summary of IPSS[1] Questionnaire at Baseline (Visit 1) (CHRONOS-A)

IPSS – urinary symptoms	Statistics	Focal	Radical	Total
Severity – n (%)	Mild = ≤ 7	xxx (xx%)	xxx (xx%)	xxx (xx%)
	Moderate = 8-19	xxx (xx%)	xxx (xx%)	xxx (xx%)
	Severe = 20-35	xxx (xx%)	xxx (xx%)	xxx (xx%)
Summary statistics	N	xxx	xxx	xxx
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)
	Missing from eCRF – n (%)	xx (xx%)	xx (xx%)	xx (xx%)

[1]See Appendix 2 for details

Table 1. 3: Summary of Maximum Cancer Core Length (MCCL) at Pre-Enrolment Biopsy, by Treatment Arm (CHRONOS-A)

Variable	Statistics	Focal	Radical	Total
MCCL	N	xxx	xxx	xxx
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)
	Missing from eCRF – n (%)	xx (xx%)	xx (xx%)	xx (xx%)

Table 1. 4: Summary of Maximum Cancer Core Length (MCCL) at Pre-Enrolment Biopsy, by Gleason Grade Group (CHRONOS-A)

Gleason Grade	Statistics	MCCL
3+3	N	xxx
	Mean (SD)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx, xx.xx)
	Missing from eCRF – n (%)	xx (xx%)
3+4	N	xxx
	Mean (SD)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx, xx.xx)
	Missing from eCRF – n (%)	xx (xx%)
3+5	N	xxx
	Mean (SD)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx, xx.xx)
	Missing from eCRF – n (%)	xx (xx%)
4+3	N	xxx
	Mean (SD)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx, xx.xx)
	Missing from eCRF – n (%)	xx (xx%)
4+4	N	xxx
	Mean (SD)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx, xx.xx)
	Missing from eCRF – n (%)	xx (xx%)
4+5	N	xxx
	Mean (SD)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx, xx.xx)

	Missing from eCRF – n (%)	xx (xx%)
5+3	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)
5+4	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)
5+5	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)
Total	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)

Table 1. 5: Baseline Characteristics (CHRONOS-B)

Variable	Statistics	Focal + finasteride	Focal + bilutamide	Focal alone	Total
Age	N	xxx	xxx	xxx	xxx
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)
	Missing from eCRF – n (%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Ethnicity – n (%)	N	xxx	xxx	xxx	xxx
	White	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Mixed	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Asian	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Black	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Other	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Missing from eCRF	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
IMD Decile – n (%)	N	xxx	xxx	xxx	xxx
	1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	2	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	3	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	4	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	5	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	6	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	7	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	8	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	9	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	10	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Missing from eCRF	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Digital Rectal Examination – n (%)	N	xxx	xxx	xxx	xxx
	Yes:	xx (xx%):	xx (xx%):	xx (xx%):	xx (xx%):
	Normal findings[1]	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Abnormal findings[1]	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	No	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Missing from eCRF	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Current medications – n (%)	N	xxx	xxx	xxx	xxx
	Yes	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	No	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Missing from eCRF	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
5 alpha-reductase inhibitor[2] – n (%)	N	xxx	xxx	xxx	xxx
	Yes over (or equal to) 6 months ago	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Yes within 6 months	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	No	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Missing from eCRF	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Stratification factors					
Tumour grade (n (%))	Gleason 3+3	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Gleason 3+4	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Gleason 4+3	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Local stage (n (%))	Clinical T2/Radiological stage <T3a	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Radiological T3a	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

[1]Proporiton out of the total number of men who had a DRE

[2]Proportion out of the total number of men who are taking current medications

Table 1. 6: Summary of IPSS[1] Score at Baseline (Visit 1) (CHRONOS-B)

IPSS – urinary symptoms	Statistics	Focal + finasteride	Focal + bilutamide	Focal alone	Total
Severity – n (%)	Mild = ≤ 7	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
	Moderate = 8-19	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
	Severe = 20-35	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Summary statistics	N	xxx	xxx	xxx	xxx
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)
	Missing from eCRF – n (%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

[1]See Appendix 2 for details

Table 1. 7: Summary of Maximum Cancer Core Length (MCCL) at Pre-Enrolment Biopsy, by Treatment Arm (CHRONOS-B)

Variable	Statistics	Focal + finasteride	Focal + bilutamide	Focal alone	Total
MCCL	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)	xxx xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)

Table 1. 8: Summary of Maximum Cancer Core Length (MCCL) at Pre-Enrolment Biopsy, by Gleason Grade Group (CHRONOS-B)

Gleason Grade	Statistics	MCCL
3+3	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)
3+4	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)
3+5	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)
4+3	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)
4+4	N Mean (SD) Median (IQR)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx)

	Missing from eCRF – n (%)	xx (xx%)
4+5	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)
5+3	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)
5+4	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)
5+5	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)
Total	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx%)

9.10.2. Analysis of Primary End Points

Table 2. 1: Proportions of patients recruited to CHRONOS-A and CHRONOS-B

CHRONOS-A	CHRONOS-B	Total
xxx (xx.x%)	xxx (xx.x%)	xxx (100.0%)

Table 2. 2: Mean number of patients recruited and randomised per month per centre (CHRONOS-A and CHRONOS-B)

	Centre	Recruited	Randomised
CHRONOS-A	…	xx.xx	xx.xx
	…	xx.xx	xx.xx
	…	xx.xx	xx.xx
	…	xx.xx	xx.xx
	…	xx.xx	xx.xx
	…	xx.xx	xx.xx
	…	xx.xx	xx.xx
	Total	xxx	xxx
CHRONOS-B	…	xx.xx	xx.xx
	…	xx.xx	xx.xx
	…	xx.xx	xx.xx
	…	xx.xx	xx.xx
	…	xx.xx	xx.xx
	…	xx.xx	xx.xx
	Total	xxx	xxx

Table 2. 3: Recruitment and randomisation rates (CHRONOS-A and CHRONOS-B), and their corresponding 95% confidence intervals

	Recruitment Rate[1]	Randomisation Rate[1]
CHRONOS-A	xx.x% (xxx/xxx) x.xx to x.xx	xx.x% (xxx/xxx) x.xx to x.xx
CHRONOS-B	xx.x% (xxx/xxx) x.xx to x.xx	xx.x% (xxx/xxx) x.xx to x.xx

[1]Rate calculated out of total number of people approached

Table 2. 4: Summary statistics for time between consent and randomisation (Days), and between randomisation and treatment (Days), by treatment arm (CHRONOS-A)

Time between (Days)	Statistics	Focal	Radical	Total
Consent – Randomisation	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Randomisation – Treatment	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)

Table 2. 5: Summary statistics for time between consent and randomisation (Days), between randomisation and treatment (Days), between randomisation and neoadjuvant drug treatment (Days), and between start of neoadjuvant drug treatment and start of focal therapy (Days), by treatment arm (CHRONOS-B)

Time between (Days)	Statistics	Focal alone	Focal + finasteride	Focal + bicalutimide	Total
Consent – Randomisation	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Randomisation – Treatment	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Randomisation-Neoadjuvant Drug Treatment	N Mean (SD) Median (IQR) Missing – n (%)	-	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Start of Neoadjuvant Drug Treatment – Focal Therapy	N Mean (SD) Median (IQR) Missing – n (%)	-	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)

Table 2. 6: Summary statistics of time between consecutive visits (Days) from Screening Visit 1 to Visit 4[1], by treatment arm (CHRONOS-A)

Visits	Statistics	Focal	Radical	Total
Screening Visit 1 – Visit 2	N Min Mean (SD) Median (IQR) Max Missing from eCRF – n (%)	xxx xx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx xx (xx.x%)	xxx xx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx xx (xx.x%)	xxx xx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx xx (xx.x%)
Visit 2 – Visit 3	N Min Mean (SD) Median (IQR) Max	xxx xx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx xx (xx.x%)	xxx xx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx xx (xx.x%)	xxx xx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx xx (xx.x%)

	Missing from eCRF – n (%)			

[1]Patients are expected to have reached Visit 3 by the end of the feasibility phase

Table 2. 7: Summary statistics of time between consecutive visits (Days) from Screening Visit 1 to Visit 4[1], by treatment arm (CHRONOS-B)

Visits	Statistics	Focal + finasteride	Focal + bilutamide	Focal alone	Total
Screening Visit 1 – Visit 2	N Min Mean (SD) Median (IQR) Max Missing from eCRF – n (%)	xxx xx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx xx (xx.x%)	xxx xx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx xx (xx.x%)	xxx xx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx xx (xx.x%)	xxx xx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx xx (xx.x%)
Visit 2 – Visit 3	N Min Mean (SD) Median (IQR) Max Missing from eCRF – n (%)	xxx xx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx xx (xx.x%)	xxx xx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx xx (xx.x%)	xxx xx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx xx (xx.x%)	xxx xx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx xx (xx.x%)

[1]Patients are expected to have reached Visit 3 by the end of the feasibility phase

Table 2. 8: Treatment compliance (CHRONOS-A)[1], and corresponding 95% confidence intervals

Treatment compliance	Focal	Radical	Total
Underwent treatment – n (%)	xx (xx.x%) x.xx to x.xx	xx (xx.x%) x.xx to x.xx	xx (xx.x%) x.xx to x.xx

[1]Data recorded at Visit 2

Table 2. 9: Treatment compliance (CHRONOS-B)[1], and corresponding 95% confidence intervals

Treatment compliance	Focal + finasteride	Focal + bilutamide	Focal alone	Total
Underwent treatment – n (%)	xx (xx.x%) x.xx to x.xx	xx (xx.x%) x.xx to x.xx	xx (xx.x%) x.xx to x.xx	xx (xx.x%) x.xx to x.xx

[1]Data recorded at Visit 3

Table 2. 10: Drug compliance (CHRONOS-B)[1]

Drug compliance	Focal + finasteride	Focal + bilutamide	Focal alone	Total
Returned empty blister packs– n (%)	xx (xx.x%) x.xx to x.xx	xx (xx.x%) x.xx to x.xx	-	xx (xx.x%) x.xx to x.xx

Received drug and did not have a registered protocol deviation that stated that the drug was taken for less than 8 weeks - n (%)	xx (xx.x%) x.xx to x.xx	xx (xx.x%) x.xx to x.xx	-	xx (xx.x%) x.xx to x.xx

[1]Data recorded at Visit 2 and 3

Table 2. 11: Reasons for ineligibility (CHRONOS-A and CHRONOS-B)

	Reasons for ineligibility	CHRONOS-A	CHRONOS-B
Violate inclusion criteria	Histologically proven prostate adenocarcinoma	xx (xx.x%)	xx (xx.x%)
	PSA ≤ 20ng/ml	xx (xx.x%)	xx (xx.x%)
	Patients must have undergone a diagnostic pre-biopsy MRI compliant with national uro-radiology consensus guidelines	xx (xx.x%)	xx (xx.x%)
	Overall Gleason score of 7 or any length of Gleason 3+3=6 provided ≥ 6mm cancer core length in any core	xx (xx.x%)	xx (xx.x%)
	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 Secondary areas of Gleason 3+3=6 or ≤ 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	xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%)	xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%)
	If radiological stage T2b/T3a is reported, has a central review regarding suitability for focal therapy taken place?	Xx (xx.x%)	xx (xx.x%)
	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	xx (xx.x%)	xx (xx.x%)
	Age at least 18 years of age	xx (xx.x%)	xx (xx.x%)
	Participants must be fit to undergo all procedures listed in the protocol as judged by clinical team	xx (xx.x%)	xx (xx.x%)
	Total violations of inclusion criteria	xx (xx.x%)	xx (xx.x%)
Violate exclusion criteria	Patient unable to give informed consent	xx (xx.x%)	xx (xx.x%)
	Life expectancy is likely to be less than 10 years	xx (xx.x%)	xx (xx.x%)
	Any previous treatment for prostate cancer	xx (xx.x%)	xx (xx.x%)
	Previous or current LHRH agonist or LHRH antagonist or anti-androgen use in CHRONOS-B	-	xx (xx.x%)
	Patients already established on a 5 alpha-reductase (finasteride or dutasteride) who wish to go into CHRONOS-B will need to discontinue this for at least 6 months prior to randomisation	-	xx (xx.x%)
	Total	xx (xx.x%)	xx (xx.x%)

Table 2. 12: Reasons for withdrawal (CHRONOS-A and CHRONOS-B)

Reasons for withdrawal	CHRONOS-A	CHRONOS-B
Screening Failure	xx (xx.x%)	xx (xx.x%)
Adverse/Serious Adverse Event	xx (xx.x%)	xx (xx.x%)
Termination of study by sponsor	xx (xx.x%)	xx (xx.x%)

Investigator decision: Protocol non-compliance Clinical decision	xx (xx.x%) xx (xx.x%) xx (xx.x%)	xx (xx.x%) xx (xx.x%) xx (xx.x%)
Lost to follow up	xx (xx.x%)	xx (xx.x%)
Withdrawal of consent	xx (xx.x%)	xx (xx.x%)
Death	xx (xx.x%)	xx (xx.x%)
Other: … … …	xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%)	xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%)
Total	xx (xx.x%)	xx (xx.x%)

Table 2. 13: Baseline characteristics, by treatment arm, for patients who withdrew from CHRONOS-A

See output of Table 1. 1, but for patients who withdrew from CHRONOS-A.

Table 2. 14: Baseline characteristics, by treatment arm, for patients who completed CHRONOS-A

See output of Table 1. 1, but for patients who completed CHRONOS-A.

Table 2. 15: Baseline characteristics, by treatment arm, for patients who withdrew from CHRONOS-B

See output of Table 1. 5, but for patients who withdrew from CHRONOS-B.

Table 2. 16: Baseline characteristics, by treatment arm, for patients who completed CHRONOS-B

See output of Table 1. 5, but for patients who completed CHRONOS-B.

Table 2. 17: Listing of all Adverse Events*

Treatment group	Subject ID	Site	AE Number	AE Term	Onset Date	End Date	Ongoing	Severity	Severity Grade	Relationship to Study IMP	Action Taken Concerning Study IMP	Outcome	Serious?

*Report adverse events for CHRONOS-A and CHRONOS-B separately

Table 2. 18: Summary of Adverse Events[2] by Severity Grade (v4.0 CTCAE), by Treatment Arm*

	Subjects with AEs[1]					
Treatment	**1**	**2**	**3**	**4**	**5**	**Total**
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Total	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**

	All AEs					
Treatment	**1**	**2**	**3**	**4**	**5**	**Total**
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Total	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**

*Report adverse events for CHRONOS-A and CHRONOS-B separately

[1]Where subjects have more than one AE, the highest severity grade has been used

[2]Expected adverse events which will not be reported are listed in Appendix 1

Table 2. 19: Number of Adverse Events[2] by Relationship to study treatment, by Treatment Arm*

	Subjects with AEs[1]						
Treatment	**Definitely**	**Probably**	**Possibly**	**Unlikely**	**Not related**	**Not assessable**	**Total**
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Total	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**

	All AEs						
Treatment	**Definitely**	**Probably**	**Possibly**	**Unlikely**	**Not related**	**Not assessable**	**Total**
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
All subjects	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**

*Report adverse events for CHRONOS-A and CHRONOS-B separately

[1]Where subjects have more than one AE, the highest relationship has been used

[2]Expected adverse events which will not be reported are listed in Appendix 1

Table 2. 20: Listing of all Serious Adverse Events by Category*

Treatment group	Subject ID	Site	SAE number	SAE term	SAE Description	Date of notification	Why was the event serious?	Date of onset	Severity	Outcome	Date of outcome	Causal relationship to event	Expectedness	Action taken

*Report serious adverse events for CHRONOS-A and CHRONOS-B separately

Table 2. 21: Summary of Serious Adverse Events by Category, by Treatment Arm*

	Subjects with SAEs					
Treatment	**Resulted in death**	**Life threatening**	**Required inpatient hospitalisation or prolongation of existing hospitalisation**	**Resulted in persistent or significant disability/incapacity**	**Resulted in congenital anomaly/birth defect**	**Other medically important event**
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Total	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**

	All SAEs					
Treatment	**Resulted in death**	**Life threatening**	**Required inpatient hospitalisation or prolongation of existing hospitalisation**	**Resulted in persistent or significant disability/incapacity**	**Resulted in congenital anomaly/birth defect**	**Other medically important event**
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Total	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**

*Report serious adverse events for CHRONOS-A and CHRONOS-B separately

Table 2. 22: Number of Serious Adverse Events by Causality Relationship to event, by Treatment Arm*

	Subjects with SAEs						
Treatment	**Definitely**	**Probably**	**Possibly**	**Unlikely**	**Not related**	**Not assessable**	**Total**
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Total	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**

	All SAEs						
Treatment	**Definitely**	**Probably**	**Possibly**	**Unlikely**	**Not related**	**Not assessable**	**Total**
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
…	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Total	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**	**xxx (xx%)**

*Report serious adverse events for CHRONOS-A and CHRONOS-B separately

9.10.3. Analysis of Secondary End Points

Table 3. 1: Summary statistics of EQ-5D-5L[1] dimensions and levels, by treatment arm (CHRONOS-A)*

Focal					
	Mobility n (%)	**Self-care n (%)**	**Usual activities n (%)**	**Pain/discomfort n (%)**	**Anxiety/depression n (%)**
Level 1	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 2	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 3	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 4	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 5	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Total	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Radical					
	Mobility n (%)	**Self-care n (%)**	**Usual activities n (%)**	**Pain/discomfort n (%)**	**Anxiety/depression n (%)**
Level 1	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 2	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 3	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 4	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 5	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Total	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)

*Repeat for all time points (screening, 3 months)

[1]See Appendix 2 for details

Table 3. 2: Summary statistics for EQ VAS (EQ-5D-5L)[1], by treatment arm (CHRONOS-A)*

	Statistics	**Focal**	**Radical**	**Total**
EQ VAS	N	xxx	xxx	xxx
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx to xx.xx)	xx.xx (xx.xx to xx.xx)	xx.xx (xx.xx to xx.xx)
	Missing – n (%)	xx (xx%)	xx (xx%)	xx (xx%)

*Repeat for all time points (screening, 3 months)

[1]See Appendix 2 for details

Table 3. 3: Summary statistics of IIEF15[1] domains, by treatment arm (CHRONOS-A)*

IIEF15 Domains	Statistics	Focal	Radical	Total
Erectile Function[1]	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Orgasmic Function[2]	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Sexual Desire[3]	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Intercourse Satisfaction[4]	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Overall Satisfaction[5]	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)

*Repeat for all time points (screening, 3 months)

[1]See Appendix 2 for details

Table 3. 4: Summary statistics of EPIC-26[1] domains, by treatment arm (CHRONOS-A)*

EPIC-26 Domains	Statistics	Focal	Radical	Total
Urinary Incontinence	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Urinary Irritative/ Obstructive	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Bowel	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Sexual	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Hormonal	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)

*Repeat for all time points (screening, 3 months)

[1]See Appendix 2 for details

Table 3. 5: Summary statistics of EPIC-URINARY DOMAIN[1] subscales, by treatment arm (CHRONOS-A)*

EPIC-URINARY DOMAIN subscales	Statistics	Focal	Radical	Total
Function	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Bother	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Incontinence	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Irritative/Obstructive	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)

*Repeat for all time points (screening, 3 months)

[1]See Appendix 2 for details

Table 3. 6: Summary statistics of EQ-5D-5L[1] dimensions and levels, by treatment arm (CHRONOS-B)*

Focal alone					
	Mobility n (%)	**Self-care n (%)**	**Usual activities n (%)**	**Pain/discomfort n (%)**	**Anxiety/depression n (%)**
Level 1	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 2	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 3	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 4	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 5	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Total	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Focal + finasteride					
	Mobility n (%)	**Self-care n (%)**	**Usual activities n (%)**	**Pain/discomfort n (%)**	**Anxiety/depression n (%)**
Level 1	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 2	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 3	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 4	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 5	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Total	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Focal + bicalutimide					
	Mobility n (%)	**Self-care n (%)**	**Usual activities n (%)**	**Pain/discomfort n (%)**	**Anxiety/depression n (%)**
Level 1	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 2	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 3	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 4	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Level 5	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Total	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)

*Repeat for all time points (screening, 3 months)

[1]See Appendix 2 for details

Table 3. 7: Summary statistics for EQ VAS (EQ-5D-5L)[1], by treatment arm (CHRONOS-B)*

	Statistics	**Focal alone**	**Focal + finasteride**	**Focal + bicalutimide**	**Total**
EQ VAS	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)

*Repeat for all time points (screening, 3 months)

[1]See Appendix 2 for details

Table 3. 8: Summary statistics of IIEF15[1] domains, by treatment arm (CHRONOS-B)*

IIEF15 Domains	Statistics	Focal alone	Focal + finasteride	Focal + bicalutimide	Total
Erectile Function	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Orgasmic Function	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Sexual Desire	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Intercourse Satisfaction	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Overall Satisfaction	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)

*Repeat for all time points (screening, 3 months)

[1]See Appendix 2 for details

Table 3. 9: Summary statistics of EPIC-26[1] domains, by treatment arm (CHRONOS-B)*

EPIC-26 Domains	Statistics	Focal alone	Focal + finasteride	Focal + bicalutimide	Total
Urinary Incontinence	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Urinary Irritative/Obstructive	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Bowel	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Sexual	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Hormonal	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)

*Repeat for all time points (screening, 3 months)

[1]See Appendix 2 for details

Table 3. 10: Summary statistics of EPIC-URINARY DOMAIN[1] subscales, by treatment arm (CHRONOS-B)*

EPIC-URINARY DOMAIN subscales	Statistics	Focal alone	Focal + finasteride	Focal + bicalutimide	Total
Function	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Bother	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Incontinence	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Irritative/Obstructive	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)

*Repeat for all time points (screening, 3 months)

[1]See Appendix 2 for details

9.10.4. Protocol Deviations/Violations

Table 4. 1: Listing of Protocol Deviations and Violations*

Subject ID	Treatment Group	Site	Date reported	Deviation or violation	How Identified?	Description	Classification	Date of deviation/ violation	Response

*Report protocol deviations for CHRONOS-A and CHRONOS-B separately

Table 4. 2: Number of Protocol Deviations and Violations*

Type of Deviation/Violation	…	…	…	Total
Inclusion/exclusion criteria	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Study drug administration	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Sampling/laboratory measurements	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Consent issue	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Study visit windows	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
NIMP administration	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Study drug prescription	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Dispensing	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Accountability	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Compliance	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Missed study visit	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Study measurements/assessments:	xx (xx%):	xx (xx%):	xx (xx%):	xx (xx%):
Primary outcome measure	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*
Secondary outcome measure	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*
Safety outcome	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*
Device	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Equipment	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Prohibited medication/substance(s)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
AE/SAE reporting	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Blinding/unblinding	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Randomisation:	xx (xx%):	xx (xx%):	xx (xx%):	xx (xx%):
(Reason for deviation)	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*
(Reason for deviation)	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*
Implementation of document prior to research approval	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Licence/certification/calibration/servicing (labs and equipment)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Delegation log/authorisation	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

Dose interruptions/modifications not specified in protocol	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Variation in clinical management of participant	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Withdrawal issue	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Falsifying research or medical records	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Repeated protocol deviations (of same type)	xx (xx%):	xx (xx%):	xx (xx%):	xx (xx%):
COVID-19 Related:	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*
(Please specify)	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*
(Please specify)	xx (xx%):	xx (xx%):	xx (xx%):	xx (xx%):
Other:	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*
…	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*
…	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*
…	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*	*xx (xx%)*
…				
Total	**xx (xx%)**	**xx (xx%)**	**xx (xx%)**	**xx (xx%)**

*Report protocol deviations for CHRONOS-A and CHRONOS-B separately

9.11. Figures to present

- Graph displaying recruitment rate over time (CHRONOS-A and CHRONOS-B)
- Graph displaying actual vs target recruitment rate over time (CHRONOS-A and CHRONOS-B)
- Graph displaying randomisation rate over time (CHRONOS-A and CHRONOS-B)
- Kaplan-Meier plots displaying withdrawal over time (CHRONOS-A and CHRONOS-B)
- Histograms of EQ-5D-5L dimensions and levels at each time point for each treatment group (CHRONOS-A and CHRONOS-B)
- Histograms of EQ VAS at each time point for each treatment group (CHRONOS-A and CHRONOS-B)
- Histograms of IIEF15 domains at each time point for each treatment group (CHRONOS-A and CHRONOS-B)
- Histograms of EPIC-26 domains at each time point for each treatment group (CHRONOS-A and CHRONOS-B)
- Histograms of EPIC-URINARY DOMAIN subscales at each time point for each treatment group (CHRONOS-A and CHRONOS-B).

10. Impact of the Covid-19 Pandemic

10.1. Analysis Populations

On 05/03/2020, Covid-19 was added to Public Health England's list of notifiable diseases in England and Wales (11).

Analysis Population	Population Definition	End Points
• Patients randomised before the Covid-19 pandemic • Patients randomised during/after the Covid-19 pandemic	• Patients randomised to the trial before 05/03/2020 • Patients randomised to the trial on/after 05/03/2020	• Baseline demographics • Recruitment rate • Reasons for ineligibility • Time between consent and randomisation
• Patients who underwent radical or focal treatment before the Covid-19 pandemic • Patients who underwent radical or focal treatment during/after the Covid-19 pandemic	• Patients whose radical or focal treatment start date is before 05/03/2020 • Patients whose radical or focal treatment start date is on/after 05/03/2020	• Time between randomisation and treatment • Treatment compliance (CHRONOS-A and CHRONOS-B)
• Patients who started neoadjuvant drug treatment before the Covid-19 pandemic • Patients who started neoadjuvant drug treatment during/after the Covid-19 pandemic	• Patients whose neoadjuvant drug treatment start date is before 05/03/2020 (CHRONO-B only) • Patients whose neoadjuvant drug treatment start date is on/after 05/03/2020 (CHRONOS-B only)	• Drug compliance (CHRONOS-B)
• Patients who underwent their most recent consecutive visits before the Covid-19 pandemic • Patients who underwent their most recent consecutive visits during/after the Covid-19 pandemic	• Patients whose most recent date of visit is before 05/03/2020 • Patients whose most recent date of visit is on/after 05/03/2020	• Time between consecutive visits
• Patients who attended the visit in question before Covid-19 pandemic • Patients who attended the visit in question after the Covid-19 pandemic	• Patients whose date of visit is before 05/03/2020 • Patients whose date of visit is on/after 05/03/2020	• Proportions of patients with missing or delayed visits
• Patients who withdrew from the trial before the Covid-19 pandemic • Patients who withdrew during/after the Covid-19 pandemic	• Patients whose withdrawal date if before 05/03/2020 • Patients whose withdrawal date is on/after 05/03/2020	• Reasons for withdrawal

The following analyses will only be presented is there exist patients in both the before and during/after Covid-19 pandemic populations. Analyses for populations which do not contain any patients will be omitted as they are already included in the main analysis outlined in Section 9.

10.2. Baseline Demographics

Patient characteristics will be summarised by treatment arm, for each of the analysis populations defined above (Section 10.1). Summaries of continuous variables will be presented as means and standard deviations if normally distributed, and as medians and inter-quartile ranges for skewed data; categorical variables will be presented as frequencies and percentages.

10.3. Analysis Summary

End Points	Outcome/Variable	Analysis	Population

Feasibility and acceptance of randomisation (rate per-month per-centre averaged) and compliance to allocated arm	Recorded data on whether patients have been (CONSORT):
	• Recruited
	• Enrolled and consented
	• Randomised
	• Withdrawn/Lost to follow-up
	• In follow-up (and what stage of follow-up)
	• Completed
	
	• Days between consent and randomisation
	
	• Reasons for ineligibility
		• Mean number of patients recruited per month per centre
		• Recruitment rate
		  • Graph displaying recruitment rate over time
		  • Graph of actual vs target recruitment rate over time
		
		• Mean number of patients randomised per month per centre
		• Randomisation rate
		  • Graph displaying randomisation rate over time
		
		• Summary statistics for time between consent and randomisation
		
		• Reasons for ineligibility
			• All randomised patients before Covid-19
			
			• All randomised patients during/after Covid-19

	• Days between randomisation and start of treatment • Days between randomisation and start of neoadjuvant drug treatment (CHRONOS-B) • Days between start of neoadjuvant drug treatment and start of focal therapy (CHRONOS-B) • Treatment details (as recorded at Visit 2)	• Summary statistics for time between randomisation and treatment • Summary statistics for time between randomisation and start of neoadjuvant treatment (CHRONOS-B only) • Summary statistics for time between start of neoadjuvant treatment and start of focal therapy (CHRONOS-B only) • Treatment compliance:	• Patients who started treatment before Covid-19 • Patients who started treatment during/after Covid-19

		○ Proportions of patients who underwent their allocated treatment (Visit 2)	
	• Treatment details (as recorded at Visit 2/3) • Protocol deviations for treatment compliance	• Drug compliance (CHRONOS-B only): ○ Proportions of patients returned their empty blister packs (yes/no) (recorded at Visit 3) ○ Proportions of patients who were given the drug and do not have a registered protocol deviations stating that the drug was taken for less than 8 weeks	• Patients who started neoadjuvant drug treatment before Covid-19 (CHRONOS-B only) • Patients who started neoadjuvant drug treatment during/after Covid-19 (CHRONOS-B only)
	• Date of visit	• Summary statistics for time between consecutive visits	• Patients who underwent their most recent of the consecutive visits before Covid-19 • Patients who underwent their most recent of the consecutive visits during/after Covid-19
	• Date of visit	• Proportions of patients with missing or delayed visits	• Patients who underwent the visit before Covid-19 • Patients who underwent the visit during/after Covid-19
	• Reasons for withdrawal	• Reasons for withdrawal	• Patients who withdrew before Covid-19 • Patients who withdrew during/after Covid-19

All analyses will be repeated for CHRONOS-A and CHRONOS-B separately.

10.4. Analysis of End Points

The following analyses will be conducted separately for each of the two patient populations defined in the table above (Section 10.3).

The mean number of patients recruited and randomised per month, per centre (including only the months in which the centre is open and recruiting), will be calculated. Overall recruitment and randomisation rates will also be calculated, along with their corresponding 95% confidence intervals. Recruitment rate is calculated as the number of participants recruited out of the total number approached. Randomisation rate is calculated as the number of participants randomised out of the total number recruited. Graphs displaying the recruitment and randomisation rates over time will be presented. A graph displaying the actual vs target recruitment rates will also be presented. These analyses will be conducted for CHRONOS-A and CHRONOS-B.

Compliance will be summarised using summary statistics, by treatment arm, for the time between consecutive visits, from screening visit to final follow-up visit (Visit 3 for feasibility phase). The proportions of patients, in each treatment arm, with a missing or delayed visit will also be presented. A missed visit is a visit at which no information was collected. A delayed visit is a visit which is outside of the visit window defined in the Visit Schedule (Section 6.7.2). These statistics will be presented for CHRONOS-A and CHRONOS-B.

Summary statistics for time between consent and randomisation, and randomisation and treatment will be presented by treatment arm. Summary statistics will also be presented for time between consecutive visits, by treatment arm.

For CHRONOS-B only, summary statistics will also be presented for time between randomisation and start of neoadjuvant treatment, and time between start of neoadjuvant treatment and start of focal therapy.

Treatment, for CHRONOS-A and CHRONOS-B, is recorded at Visit 2 (Treatment Visit). For focal therapy arms (CHRONOS-A (Focal arm) and CHRONOS-B) treatment is recorded by date of treatment and completed treatment details at Visit 2. For the radical arm of CHRONOS-A, treatment is recorded by date of visit 2 and completed treatment details on Radiotherapy/Brachytherapy Log and Prostatectomy Log at Visit 2. The proportions of patients in each treatment arm who underwent treatment will be presented, along with their corresponding 95% confidence intervals.

Treatment compliance will be evaluated by arm and by trial (CHRONOS-A/CHRONOS-B). Viable treatment compliance is defined as the lower end of the confidence interval for the proportion of patients who underwent treatment being ≥80%. If the lower end of the confidence interval for the proportion of patients who underwent treatment is ≥80%, then we have viable compliance to progress to the main phase. If the lower end of the confidence interval for the proportion of patients who underwent treatment is between 70% and 80%, then this indicates that remedial work is needed to improve this for the main stage. If the lower end of the confidence interval for the proportion of patients who underwent treatment is < 70%, then this could affect the primary outcome analysis and threaten the validity of the study. Data will be presented to the TSC for a final decision in this case.

Neoadjuvant drug treatment in CHRONOS-B is prescribed at randomisation. Drug compliance will be estimated using two definitions:

- Patients who returned their empty blister packs (yes/no) at Visit 3
- Patients who took the drug and did not have a registered protocol deviation stating that they took the drug for less than 8 weeks.

For CHRONOS-B only, the proportions of patients who returned their empty blister packs (yes/no), and the proportions of patients who took the drug and did not have a registered protocol deviation stating that they took the drug for less than 8 weeks, in each treatment arm will be reported, along with their corresponding 95% confidence intervals. Drug compliance will be evaluated by arm and by trial for each of the drug compliance definitions. Viable drug compliance is defined as the lower end of the confidence interval for the proportions being ≥ 90%. If the lower end of the confidence interval for the proportions is between 80% and 90%, then this indicates that remedial work is needed to improve this for the main stage. If the lower end of the confidence interval for the

proportions is < 80%, then this could affect the primary outcome analysis and threaten the validity of the study, and may require sample size re-estimation. Data for both drug compliance definitions will be presented to the TSC for a final decision in this case.

The reasons for ineligibility and withdrawal will be collected and recorded for CHRONOS-A and CHRONOS-B separately.

10.5. Covid-19 Related Protocol Deviations

Covid-19 related protocol deviations will be listed and summarised as per Section 9.9, using Table 4.1 and Table 4.2 from Section 9.10.4.

10.6. Tables to Present

10.6.1. Baseline Characteristics

Table 5. 1: Baseline characteristics, by treatment arm, for patients recruited to the trial before[1] the Covid-19 pandemic (CHRONOS-A)

See output of Table 1. 1, but for patients recruited to CHRONOS-A before[1] the Covid-19 pandemic.

[1]Patients were recruited before the Covid-19 pandemic if they were recruited to CHRONOS-A before 05/03/2020 (see Section 10.1)

Table 5. 2: Baseline characteristics, by treatment arm, for patients recruited to the trial during/after[1] the Covid-19 pandemic (CHRONOS-A)

See output of Table 1. 1, but for patients recruited to CHRONOS-A during/after[1] the Covid-19 pandemic.

[1]Patients were recruited during/after the Covid-19 pandemic if they were recruited to CHRONOS-A after 05/03/2020 (see Section 10.1)

Table 5. 3: Baseline characteristics, by treatment arm, for patients recruited to the trial before[1] the Covid-19 pandemic (CHRONOS-B)

See output of Table 1. 5, but for patients recruited to CHRONOS-B before[1] the Covid-19 pandemic.

[1]Patients were recruited before the Covid-19 pandemic if they were recruited to CHRONOS-B before 05/03/2020 (see Section 10.1)

Table 5. 4: Baseline characteristics, by treatment arm, for patients recruited to the trial during/after[1] the Covid-19 pandemic (CHRONOS-B)

See output of Table 1. 5, but for patients recruited to CHRONOS-B during/after[1] the Covid-19 pandemic.

[1]Patients were recruited during/after the Covid-19 pandemic if they were recruited to CHRONOS-B after 05/03/2020 (see Section 10.1)

10.6.2. Analysis of End Points

Table 6. 1: Mean number of patients recruited and randomised per month per centre, for patients recruited to the trial before[1] the Covid-19 pandemic (CHRONOS-A and CHRONOS-B)

See output of Table 2. 2, but for patients recruited to the trial before[1] the Covid-19 pandemic.

[1]Patients were recruited before the Covid-19 pandemic if they were recruited to the trial before 05/03/2020 (see Section 10.1)

Table 6. 2: Mean number of patients recruited and randomised per month per centre, for patients recruited to the trial during/after[1] the Covid-19 pandemic (CHRONOS-A and CHRONOS-B)

See output of Table 2. 2, but for patients recruited to the trial during/after[1] the Covid-19 pandemic.

[1]Patients were recruited during/after the Covid-19 pandemic if they were recruited to the trial after 05/03/2020 (see Section 10.1)

Table 6. 3: Recruitment and randomisation rates[1], for patients recruited to the trial before[2] the Covid-19 pandemic (CHRONOS-A and CHRONOS-B)

See output for Table 2. 3, but for patients recruited to the trial before[2] the Covid-19 pandemic.

[1]Rate calculated out of total number of people approached

[2]Patients were recruited before the Covid-19 pandemic if they were recruited to the trial before 05/03/2020 (see Section 10.1)

Table 6. 4: Recruitment and randomisation rates[1], for patients recruited to the trial during/after[2] the Covid-19 pandemic (CHRONOS-A and CHRONOS-B)

See output for Table 2. 3, but for patients recruited to the trial during/after[2] the Covid-19 pandemic.

[1]Rate calculated out of total number of people approached

[2]Patients were recruited during/after the Covid-19 pandemic if they were recruited to the trial after 05/03/2020 (see Section 10.1)

Table 6. 5: Reasons for ineligibility, for patients recruited to the trial before[1] the Covid-19 pandemic (CHRONOS-A and CHRONOS-B)

See output for Table 2. 11, but for patients recruited to the trial before[1] the Covid-19 pandemic.

[1]Patients were recruited before the Covid-19 pandemic if they were recruited to the trial before 05/03/2020 (see Section 10.1)

Table 6. 6: Reasons for ineligibility, for patients recruited to the trial during/after[1] the Covid-19 pandemic (CHRONOS-A and CHRONOS-B)

See output for Table 2. 11, but for patients recruited to the trial during/after[1] the Covid-19 pandemic.

[1]Patients were recruited during/after the Covid-19 pandemic if they were recruited to the trial after 05/03/2020 (see Section 10.1)

Table 6. 7: Reasons for withdrawal, for patients who withdrew from the trial before[1] the Covid-19 pandemic (CHRONOS-A and CHRONOS-B)

See output for Table 2. 12, but for patients who withdrew from the trial before[1] the Covid-19 pandemic.

[1]Patients were recruited before the Covid-19 pandemic if they were recruited to the trial before 05/03/2020 (see Section 10.1)

Table 6. 8: Reasons for withdrawal, for patients who withdrew from the trial during/after[1] the Covid-19 pandemic (CHRONOS-A and CHRONOS-B)

See output for Table 2. 12, but for patients who withdrew from the trial during/after[1] the Covid-19 pandemic.

[1]Patients were recruited during/after the Covid-19 pandemic if they were recruited to the trial after 05/03/2020 (see Section 10.1)

Table 6. 9: Summary statistics for time between consent and randomisation (Days), by treatment arm, for patients recruited to the trial before[1] the Covid-19 pandemic (CHRONOS-A)

Time between (Days)	Statistics	Focal	Radical	Total
Consent – Randomisation	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)

[1]Patients were recruited before the Covid-19 pandemic if they were recruited to CHRONOS-A before 05/03/2020 (see Section 10.1)

Table 6. 10: Summary statistics of time between consent and randomisation (Days), by treatment arm, for patients recruited to the trial during/after[1] the Covid-19 pandemic (CHRONOS-A)

See output for Table 6. 9, but for patients recruited to CHRONOS-A during/after[1] the Covid-19 pandemic.

[1]Patients were recruited during/after the Covid-19 pandemic if they were recruited to CHRONOS-A on/after 05/03/2020 (see Section 10.1)

Table 6. 11: Summary statistics for time between randomisation and treatment (Days), by treatment arm, for patients who underwent radical or focal treatment before the Covid-19 pandemic (CHRONOS-A)

Time between (Days)	Statistics	Focal	Radical	Total
Randomisation - Treatment	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)

[1]Patients who underwent treatment before the Covid-19 pandemic if they had a radical or focal treatment date before 05/03/2020 (see Section 10.1)

Table 6. 12: Summary statistics for time between randomisation and treatment (Days), by treatment arm, for patients who underwent radical or focal treatment during/after[1] the Covid-19 pandemic (CHRONOS-A)

See output for Table 6. 11, but for patients in CHRONOS-A who underwent radical or focal treatment during/after the Covid-19 pandemic.

[1]Patients who underwent treatment during/after the Covid-19 pandemic if they had a radical or focal treatment date on/after 05/03/2020 (see Section 10.1)

Table 6. 13: Summary statistics of time between consent and randomisation (Days), by treatment arm, for patients recruited to the trial before[1] the Covid-19 pandemic (CHRONOS-B)

Time between (Days)	Statistics	Focal alone	Focal + finasteride	Focal + bicalutimide	Total
Consent – Randomisation	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)

[1]Patients were recruited before the Covid-19 pandemic if they were recruited to CHRONOS-B before 05/03/2020 (see Section 10.1)

Table 6. 14: Summary statistics of time between consent and randomisation (Days), by treatment arm, for patients recruited to the trial during/after[1] the Covid-19 pandemic (CHRONOS-B)

See output for Table 6. 13, but for patients who were recruited to CHRONO-B during/after the Covid-19 pandemic.

[1]Patients were recruited during/after the Covid-19 pandemic if they were recruited to CHRONOS-B on/after 05/03/2020 (see Section 10.1)

Table 6. 15: Summary statistics of time between randomisation and treatment (Days), between randomisation and neoadjuvant treatment (Days), and between start of neoadjuvant treatment and start of focal therapy (Days), by treatment arm, for patients who underwent focal treatment before[1] the Covid-19 pandemic (CHRONOS-B)

Time between (Days)	Statistics	Focal alone	Focal + finasteride	Focal + bicalutimide	Total
Randomisation – Treatment	N Mean (SD) Median (IQR) Missing – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Randomisation-Neoadjuvant Drug Treatment	N Mean (SD) Median (IQR) Missing – n (%)	-	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)
Start of Neoadjuvant Drug Treatment – Focal Therapy	N Mean (SD) Median (IQR) Missing – n (%)	-	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)	xxx xx.xx (xx.xx) xx.xx (xx.xx to xx.xx) xx (xx%)

[1]Patients who underwent treatment before the Covid-19 pandemic if they had a focal treatment date before 05/03/2020 (see Section 10.1)

Table 6. 16: Summary statistics of time between randomisation and treatment (Days), between randomisation and neoadjuvant treatment (Days), and between start of neoadjuvant treatment and start of focal therapy (Days), by treatment arm, for patients who underwent focal treatment during/after[1] the Covid-19 pandemic (CHRONOS-B)

See output for

Table 6. **15**, but for patients in CHRONOS-B who underwent focal treatment during/after the Covid-19 pandemic.

[1]Patients who underwent treatment during/after the Covid-19 pandemic if they had a focal treatment date on/after 05/03/2020 (see Section 10.1)

[2]Use treatment start date if blister pack return date unknown

Table 6. 17: Summary statistics of time between consecutive visits (Days) from Screening Visit 1 to Visit 4[2], by treatment arm, for patients who underwent the most recent of the consecutive visits before[1] the Covid-19 pandemic (CHRONOS-A)

See output for Table 2. 6, but for patients in CHRONOS-A who underwent the most recent of the consecutive visits before[1] the Covid-19 pandemic.

[1]Patients underwent the most recent of the consecutive visits before the Covid-19 pandemic if the date of visit of their most recent consecutive visit was before 05/03/2020 (see Section 10.1)

[2]Patients are expected to have reached Visit 3 by the end of the feasibility phase

Table 6. 18: Summary statistics of time between consecutive visits (Days) from Screening Visit 1 to Visit 4[2], by treatment arm, for patients who underwent the most recent of the consecutive visits during/after[1] the Covid-19 pandemic (CHRONOS-A)

See output for Table 2. 6, but for patients in CHRONOS-A who underwent the most recent of the consecutive visits during/after[1] the Covid-19 pandemic.

[1]Patients underwent the most recent of the consecutive visits during/after the Covid-19 pandemic if the date of visit of their most recent consecutive visit was on/after 05/03/2020 (see Section 10.1)

[2]Patients are expected to have reached Visit 3 by the end of the feasibility phase

Table 6. 19: Summary statistics of time between consecutive visits (Days) from Screening Visit 1 to Visit 4[2], by treatment arm, for patients who underwent the most recent of the consecutive visits before[1] the Covid-19 pandemic (CHRONOS-B)

See output for Table 2. 7, but for patients in CHRONOS-B who underwent the most recent of the consecutive visits before[1] the Covid-19 pandemic.

[1]Patients underwent the most recent of the consecutive visits before the Covid-19 pandemic if the date of visit of their most recent consecutive visit was before 05/03/2020 (see Section 10.1)

[2]Patients are expected to have reached Visit 3 by the end of the feasibility phase

Table 6. 20: Summary statistics of time between consecutive visits (Days) from Screening Visit 1 to Visit 4[2], by treatment arm, for patients who underwent the most recent of the consecutive visits during/after[1] the Covid-19 pandemic (CHRONOS-B)

See output for Table 2. 7, but for patients in CHRONOS-B who underwent the most recent of the consecutive visits during/after[1] the Covid-19 pandemic.

[1]Patients underwent the most recent of the consecutive visits during/after the Covid-19 pandemic if the date of visit of their most recent consecutive visit was after 05/03/2020 (see Section 10.1)

[2]Patients are expected to have reached Visit 3 by the end of the feasibility phase

Table 6. 21: Proportions of patients, in each treatment arm, with a missing or delayed visit, for patients who underwent the visit before[1] the Covid-19 pandemic (CHRONOS-A)

Visit[2]		Focal	Radical	Total
Screening Visit 1	**Total**	xxx	xxx	xxx
	Delayed (n (%))	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	Missing (n (%))	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Visit 2	**Total**	xxx	xxx	xxx
	Delayed (n (%))	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	Missing (n (%))	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Visit 3	**Total**	xxx	xxx	xxx
	Delayed (n (%))	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	Missing (n (%))	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

[1]Patients underwent the visit before the Covid-19 pandemic if the date of visit was before 05/03/2020 (see Section 10.1)

[2]Patients are expected to have reached Visit 3 by the end of the feasibility phase

Table 6. 22: Proportions of patients, in each treatment arm, with a missing or delayed visit, for patients who underwent the visit during/after[1] the Covid-19 pandemic (CHRONOS-A)

See output for Table 6. 21, but for patients in CHRONOS-A who underwent the visit during/after[1] the Covid-19 pandemic.

[1]Patients underwent the visit during/after the Covid-19 pandemic if the date of visit was on/after 05/03/2020 (see Section 10.1)

[2]Patients are expected to have reached Visit 3 by the end of the feasibility phase

Table 6. 23: Proportions of patients, in each treatment arm, with a missing or delayed visit, for patients who underwent the visit before[1] the Covid-19 pandemic (CHRONOS-B)

Visit[2]		Focal + finasteride	Focal + bilutamide	Focal alone	Total
Screening Visit 1	**Total**	xxx	xxx	xxx	xxx
	Delayed (n(%))	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	Missing (n(%))	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Visit 2	**Total**	xxx	xxx	xxx	xxx
	Delayed (n(%))	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	Missing (n(%))	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Visit 3	**Total**	xxx	xxx	xxx	xxx
	Delayed (n(%))	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
	Missing (n(%))	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

[1]Patients underwent the visit before the Covid-19 pandemic if the date of visit was before 05/03/2020 (see Section 10.1)

[2]Patients are expected to have reached Visit 3 by the end of the feasibility phase

Table 6. 24: Proportions of patients, in each treatment arm, with a missing or delayed visit, for patients who underwent the visit during/after[1] the Covid-19 pandemic (CHRONOS-B)

See output for

Table 6. 23, but for patients in CHRONOS-B who underwent the visit during/after[1] the Covid-19 pandemic.

[1]Patients underwent the visit during/after the Covid-19 pandemic if the date of visit was on/after 05/03/2020 (see Section 10.1)

[2]Patients are expected to have reached Visit 3 by the end of the feasibility phase

Table 6. 25: Treatment compliance (CHRONOS-A)[1], for patients who underwent radical or focal treatment before[2] the Covid-19 pandemic

See output for Table 2. 8, but for patients in CHRONOS-A who underwent radical or focal treatment before[2] the Covid-19 pandemic.

[1]Data recorded at Visit 2

[2]Patients underwent treatment before the Covid-19 pandemic if their date of radical or focal treatment was before 05/03/2020 (see Section 10.1)

Table 6. 26: Treatment compliance (CHRONOS-A)[1], for patients who underwent radical or focal treatment during/after[2] the Covid-19 pandemic

See output for Table 2. 8, but for patients in CHRONOS-A who underwent radical or focal treatment during/after[2] the Covid-19 pandemic.

[1]Data recorded at Visit 2

[2]Patients underwent treatment before the Covid-19 pandemic if their date of radical or focal treatment was on/after 05/03/2020 (see Section 10.1)

Table 6. 27: Treatment compliance (CHRONOS-B)[1], for patients who underwent focal treatment before[2] the Covid-19 pandemic

See output for Table 2. 9, but for patients in CHRONOS-B who underwent focal treatment before[2] the Covid-19 pandemic.

[1]Data recorded at Visit 2

[2]Patients underwent treatment before the Covid-19 pandemic if their date of focal treatment was before 05/03/2020 (see Section 10.1)

Table 6. 28: Treatment compliance (CHRONOS-B)[1], for patients who underwent focal treatment during/after[2] the Covid-19 pandemic

See output for Table 2. 9, but for patients in CHRONOS-B who underwent focal treatment during/after[2] the Covid-19 pandemic.

[1]Data recorded at Visit 2

[2]Patients underwent treatment before the Covid-19 pandemic if their date of focal treatment was on/after 05/03/2020 (see Section 10.1)

Table 6. 29: Drug compliance (CHRONOS-B)[1], for patients who started neoadjuvant drug treatment before[2] the Covid-19 pandemic

See output for Table 2. 10, but for patients in CHRONOS-B who underwent neoadjuvant drug treatment before[2] the Covid-19 pandemic.

[1]Data recorded at Visit 2 and 3

[2]Patients underwent treatment before the Covid-19 pandemic if their date of neoadjuvant drug treatment was before 05/03/2020 (see Section 10.1)

Table 6. 30: Drug compliance (CHRONOS-B)[1], for patients who started neoadjuvant drug treatment during/after[2] the Covid-19 pandemic

See output for Table 2. 10, but for patients in CHRONOS-B who underwent neoadjuvant drug treatment during/after[2] the Covid-19 pandemic.

[1]Data recorded at Visit 2 and 3

[2]Patients underwent treatment before the Covid-19 pandemic if their date of neoadjuvant drug treatment was on/after 05/03/2020 (see Section 10.1)

10.8. Figures to Present

- Graph displaying recruitment rate over time (CHRONOS-A and CHRONOS-B), for patients recruited to the trial before[1] the Covid-19 pandemic
- Graph displaying recruitment rate over time (CHRONOS-A and CHRONOS-B), for patients recruited to the trial during/after[2] the Covid-19 pandemic
- Graph displaying actual vs target recruitment rate over time (CHRONOS-A and CHRONOS-B), for patients recruited to the trial before[1] the Covid-19 pandemic
- Graph displaying actual vs target recruitment rate over time (CHRONOS-A and CHRONOS-B), for patients recruited to the trial during/after[2] the Covid-19 pandemic
- Graph displaying randomisation rate over time (CHRONOS-A and CHRONOS-B), for patients recruited to the trial before[1] the Covid-19 pandemic
- Graph displaying randomisation rate over time (CHRONOS-A and CHRONOS-B), for patients recruited to the trial during/after[2] the Covid-19 pandemic.

[1]Patients were recruited before the Covid-19 pandemic if they were recruited to the trial before 05/03/2020 (see Section 10.1)

[2]Patients were recruited during/after the Covid-19 pandemic if they were recruited to the trial after 05/03/2020 (see Section 10.1).

11. Statistical Requirement for Early Termination of the Study

For a predicted sample size of 60 participants per trial (CHRONOS-A and CHRONOS-B), the 95% confidence interval for an estimated recruitment rate of 33% is (0.211, 0.449). Progression to the main stage will be initiated if the recruitment rate is above 21.1%.

If the recruitment rate is below 21.1%, the results of the feasibility analysis suggest that the trial is unfeasible and should be stopped. The result will be presented to the TSC, who will make the final decision, based on the evidence shown, as to whether the trial will continue to main stage. If the recruitment rate is between 21.1% and 33%, then remedial work will be implemented to improve the recruitment rate in the main stage of the trial. If the recruitment rate is greater than or equal to 33%, the trial will be deemed feasible.

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 with the ICE (European Registry for Cryosurgical Ablation of the prostate, EuCAP) or the HEAT international HIFU registry as per NICE guidelines IPG432/IPG42.

12. Imperial Prostate Trial Steering Committee

A combined TSC and DMEC is in place to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of Good Clinical Practice (GCP) and the relevant regulations. The TSC should agree the trial protocol and any protocol amendments and provide advice to the investigators and the Trial Management Group (TMG), via Imperial Clinical Trials Unit (ICTU) on all aspects of the trial.

The TSC should meet at least annually, although there may be periods when more frequent meetings are necessary.

13. Amendments to Version 1.0

14. References

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15. Appendix 1 – 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. lympocoele, 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.

16. Appendix 2 – PROMS

16.1. IPSS

The International Prostate Symptom Score (I-PSS) is based on the answers to seven questions concerning urinary symptoms and one question concerning quality of life. The responses to the questions concerning urinary symptoms range from 0 to 5, indicating increasing severity of the particular symptom. Thus, the overall score can range from 0 (asymptomatic) to 35 (very symptomatic). The total score for the questions concerning urinary symptoms can be categorised as follows (12):

- Mild – symptom score less than or equal to 7
- Moderate – symptom score range 8-19
- Severe – symptom score range 20-35.

The answers to the question concerning the patient's quality of life ranges from 0 "delightful" to 6 "terrible".

16.2. EQ-5D-5L

The EQ-5D family of instruments has been developed to describe and value health across a wide range of disease areas. The EQ-5D-5L comprises of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and each dimension has five response levels: no problems, slight problems, moderate problems, severe problems, unable to/extreme problems (13).

16.2.1. EQ VAS

The EQ VAS records the respondent's overall current health on a vertical visual analogue scale, where the ends of the scale are labelled "The best health you can imagine" and "The worst health you can imagine" (13). The EQ VAS provides a quantitative measure of the patient's perception of their overall health. The EQ VAS is a continuous measure from 0 to 100.

16.3. IIEF-15

The 15-question International Index of Erectile Function (IIEF) Questionnaire is a validated, multi-dimensional, self-administered investigation that is useful in the clinical assessment of erectile dysfunction and treatment outcomes in clinical trials (14).

A score of 0-5 is awarded to each of the 15 questions that examine the 4 main domains of male sexual function: erectile function, orgasmic function, sexual desire and intercourse satisfaction (14).

Function Domain	Questions	Max score
Erectile Function	Q1, 2, 3, 4, 5, 15	30
Orgasmic Function	Q9, 10	10
Sexual Desire	Q11, 12	10
Intercourse Satisfaction	Q6, 7, 8	10
Overall Satisfaction	Q13, 14	10

16.4. EPIC-26

The Expanded Prostate Cancer Index Composite (EPIC) is a comprehensive instrument designed to evaluate patient function and bother after prostate cancer treatment. EPIC-26 was developed as a short-form version of the full EPIC. This version contains 26 items and 5 domains: urinary incontinence, urinary irritative/obstructive, bowel, sexual and hormonal. Response options

for each EPIC item form a Likert scale, and multi-item scale scores are transformed to a 0-100 scale (15). Higher scores represent higher HRQoL.

Step 1: The response for each item is standardised to a 0 to 100 scale according to the table below (15):

Question Number	Item Number	Item Response Value	Standardised Value
1, 8a, 8b, 10, 11	23, 57, 58, 60, 64	1 2 3 4 5	0 25 50 75 100
2, 9	26, 59	1 2 3 4	0 33 67 100
3	27	0 1 2 3	100 67 33 0
4a, 4b, 4c, 4d, 4e, 6a, 6b, 6c, 6d, 6e, 13a, 13b, 13c, 13d, 13e	28, 29, 30, 31, 33, 49, 50, 52, 53, 54, 74, 75, 77, 78, 79	0 1 2 3 4	100 75 50 25 0
5, 7, 12	34, 55, 68	1 2 3 4 5	100 75 50 25 0

Step 2: Using the item groupings listed below for each HRQOL Domain Score, average the standardised values for all items within a group to create the summary or subscale score. If more then 20% of the items that comprise a domain summary score or subscale score are missing a response, the corresponding domain summary or subscale score cannot be calculated (15).

Domain	Question Number	Item Number	Number of non-missing items needed to compute the score
Urinary Incontinence	1, 2, 3, 4a	23, 26-28	4
Urinary Irritative/Obstructive	4b, 4c, 4d, 4e	29-31, 33	4
Bowel	6a, 6b, 6c, 6d, 6e, 7	49, 50, 52-55	5
Sexual	8a, 8b, 9, 10, 11, 12	57-60, 64, 68	5
Hormonal	13a, 13b, 13c, 13d, 13e	74, 75, 77-79	4

16.5. EPIC – URINARY FUNCTION

The Expanded Prostate Cancer Index Composite (EPIC) is a comprehensive instrument designed to evaluate patient function and bother after prostate cancer treatment. EPIC assesses the disease-specific aspects of prostate cancer and its therapies and comprises of four summary domains (Urinary, Bowel, Sexual and Hormonal). The Urinary Domain Summary Score is split into

two distinct Incontinence and Irritative/Obstructive subscales. In addition, the Domain Score has measurable Function and Both subscale components. Response options for each EPIC item form a Likert scale, and multi-item scale scores are transformed to a 0-100 scale (15). Higher scores represent higher HRQoL.

Step 1: The response for each item is standardised to a 0 to 100 scale according to the table below (15):

Question Number	Item Number	Item Response Value	Standardised Value
1, 2, 3	23, 24, 25	1 2 3 4 5	0 25 50 75 100
4	26	1 2 3 4	0 33 67 100
5	27	0 1 2 3	100 67 33 0
6a, 6b, 6c, 6d, 6e, 6f	28, 29, 30, 31, 32, 33	0 1 2 3 4	100 75 50 25 0
7	34	1 2 3 4 5	100 75 50 25 0

Step 2: Using the item groupings listed below for each HRQOL Domain Score, average the standardised values for all items within a group to create the summary or subscale score. If more then 20% of the items that comprise a domain summary score or subscale score are missing a response, the corresponding domain summary or subscale score cannot be calculated (15).

Domain	Question Number	Item Number	Number of non-missing items needed to compute the score
Function	1, 2, 3, 4, 5	23-27	4
Bother	6a, 6b, 6c, 6d, 6e, 6f, 7	28-34	6
Incontinence	1, 4, 5, 6a	23, 26-28	4
Irritative/Obstructive	2, 3, 6b, 6c, 6d, 6e, 6f	24, 25, 29-33	6