



Clinical trial results: IP4- CHRONOS: Comparative Health Research Outcomes of NOvel Surgery in Prostate Cancer Summary

EudraCT number	2019-001365-32
Trial protocol	GB
Global end of trial date	13 January 2023

Results information

Result version number	v1 (current)
This version publication date	20 December 2024
First version publication date	20 December 2024

Trial information

Trial identification

Sponsor protocol code	19CX5006
-----------------------	----------

Additional study identifiers

ISRCTN number	ISRCTN17796995
ClinicalTrials.gov id (NCT number)	NCT04049747
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	Charing Cross Hospital Campus, Fulham Palace Road,, London, United Kingdom, W6 8RF
Public contact	Professor Hashim Ahmed, Imperial College London, hashim.ahmed@imperial.ac.uk
Scientific contact	Professor Hashim Ahmed, Imperial College London, hashim.ahmed@imperial.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 January 2023
Global end of trial reached?	Yes
Global end of trial date	13 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Our initial CHRONOS trial will be a pilot study. If successful, we will apply for funding for a full main study which will run through if and when funding is approved. We have therefore described the objectives for both phases of CHRONOS, and for both CHRONOS-A and CHRONOS-B.

Pilot study:

- 1) To determine patient acceptance to randomisation
- 2) To conduct an embedded qualitative study of patient and clinician acceptance and experience of the linked RCT CHRONOS design
- 3) To establish the feasibility of an economic evaluation alongside the main trial
- 4) To determine the acceptability and completeness of resource use and utility measures (EQ-5D-5L)
- 5) To identify the relevant NHS and non-NHS resource use to be collected alongside the main trial
- 6) To identify the relevant items to populate the Cost and Consequences framework
- 7) To perform preliminary analysis of pattern of missing data

Main study:

CHRONOS A: To evaluate cancer control rates of focal therapy compared to stan

Protection of trial subjects:

The study had a joint role of a Global Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) to provide overall supervision of the trials and ensure that it is being conducted in accordance with the principles of Good Clinical Practice (GCP) and the relevant regulations. The Global TSC/DMC would also safeguard the interests of trial participants, to ensure that the rights, safety and well-being of the trial participants were the most important consideration and would prevail over other interests. The TSC/DMC responsibilities also included monitoring the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 100
Worldwide total number of subjects	100
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	100
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The Study results are based on the Feasibility/pilot

CHRONOS-A

60 patients over 12-months

CHRONOS-B

60 patients over 12-months

(These participants will form part of the main study if feasibility is met and funding obtained for Main Phase)

Pre-assignment

Screening details:

Inclusion:

PSA \leq 20ng/ml , Diagnostic pre-biopsy MRI, Proven prostate adenocarcinoma, Overall Gleason score of 7, Age > 18 years, Fit to undergo all procedures

Exclusion:

LHRH agonist or LHRH antagonist or anti-androgen use Chronos B, Previous treatment for prostate cancer, Life expectancy less than 10 years, Unable to give informed consent

Period 1

Period 1 title	IP4-CHRONOS Pilot Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	CHRONOS-A Arm1 - Radical therapy

Arm description:

Radical therapy (prostatectomy or radiotherapy [external beam or brachytherapy]). The type of radical therapy will be determined by physician or patient preference.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Arm title	CHRONOS-A Arm 2 Focal Therapy
------------------	-------------------------------

Arm description:

Focal therapy alone (high intensity focused ultrasound [HIFU] or cryotherapy or other validated energy modality as per physician/patient decision/choice).

Arm type	Focal therapy alone
No investigational medicinal product assigned in this arm	

Arm title	CHRONOS-B Arm 1 Focal Therapy
------------------	-------------------------------

Arm description:

Focal therapy alone (high intensity focused ultrasound [HIFU] or cryotherapy or other validated energy modality as per physician and centre choice).

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Arm title	CHRONOS-B Arm 2 Focal + Finasteride
------------------	-------------------------------------

Arm description:

Neoadjuvant finasteride 5mg once daily for a minimum of 12 weeks (84 days) followed by focal therapy (as per control arm).

Arm type	Experimental
----------	--------------

Investigational medicinal product name	finasteride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

neoadjuvant finasteride 5mg once daily for a minimum of 12 weeks (84 days) followed by focal therapy (as per control arm).

Arm title	CHRONOS-B Arm 3 Focal + Bicalutamide
------------------	--------------------------------------

Arm description:

Neoadjuvant bicalutamide 50mg once daily therapy for 12 weeks (84 days) followed by focal therapy (as per control arm).

Arm type	Experimental
Investigational medicinal product name	bicalutamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Neoadjuvant bicalutamide 50mg once daily therapy for 12 weeks (84 days) followed by focal therapy (as per control arm).

Number of subjects in period 1	CHRONOS-A Arm1 - Radical therapy	CHRONOS-A Arm 2 Focal Therapy	CHRONOS-B Arm 1 Focal Therapy
Started	18	18	22
Completed	18	15	21
Not completed	0	3	1
Consent withdrawn by subject	-	3	1

Number of subjects in period 1	CHRONOS-B Arm 2 Focal + Finasteride	CHRONOS-B Arm 3 Focal + Bicalutamide
Started	21	21
Completed	21	21
Not completed	0	0
Consent withdrawn by subject	-	-

Baseline characteristics

Reporting groups

Reporting group title	CHRONOS-A Arm1 - Radical therapy
Reporting group description: Radical therapy (prostatectomy or radiotherapy [external beam or brachytherapy]). The type of radical therapy will be determined by physician or patient preference.	
Reporting group title	CHRONOS-A Arm 2 Focal Therapy
Reporting group description: Focal therapy alone (high intensity focused ultrasound [HIFU] or cryotherapy or other validated energy modality as per physician/patient decision/choice).	
Reporting group title	CHRONOS-B Arm 1 Focal Therapy
Reporting group description: Focal therapy alone (high intensity focused ultrasound [HIFU] or cryotherapy or other validated energy modality as per physician and centre choice).	
Reporting group title	CHRONOS-B Arm 2 Focal + Finasteride
Reporting group description: Neoadjuvant finasteride 5mg once daily for a minimum of 12 weeks (84 days) followed by focal therapy (as per control arm).	
Reporting group title	CHRONOS-B Arm 3 Focal + Bicalutamide
Reporting group description: Neoadjuvant bicalutamide 50mg once daily therapy for 12 weeks (84 days) followed by focal therapy (as per control arm).	

Reporting group values	CHRONOS-A Arm1 - Radical therapy	CHRONOS-A Arm 2 Focal Therapy	CHRONOS-B Arm 1 Focal Therapy
Number of subjects	18	18	22
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
log mean	68.78	69.28	64.55
standard deviation	± 7.64	± 4.60	± 7.00
Gender categorical Units: Subjects			
Female	0	0	0
Male	18	18	22
Ethnicity – n (%)			
Ethnicity – n (%)			
Units: Subjects			
White	8	13	14

Mixed	0	0	1
Asian	1	0	0
Black	0	0	1
Other	1	0	1
Not Reported	8	5	5
IMD Decile – n (%)			
Units: Subjects			
Decile 1	0	0	0
Decile 2	0	1	2
Decile 3	1	1	1
Decile 4	2	1	4
Decile 5	2	2	4
Decile 6	2	2	3
Decile 7	2	4	1
Decile 8	3	4	2
Decile 9	3	1	4
Decile 10	3	2	1
Digital Rectal Examination – n (%)			
Units: Subjects			
Normal findings	3	5	4
Abnormal findings	3	4	3
No	12	8	15
Missing from eCRF	0	1	0
Current medications			
Units: Subjects			
Yes	11	12	13
No	5	3	9
Missing from eCRF	2	3	0
5 alpha-reductase inhibitor2			
Units: Subjects			
Yes over (or equal to) 6 months ago	0	0	0
Yes within 6 months	0	1	0
No	16	14	22
Missing from eCRF	2	3	0
Tumour grade			
Units: Subjects			
Gleason 3+3	1	1	2
Gleason 3+4	14	13	16
Gleason 4+3	3	4	4
Local stage			
Units: Subjects			
Clinical T2/Radiological stage <T3a	18	18	20
Radiological T3a	0	0	2
Previous or current 5ARI use?			
Units: Subjects			
Yes	0	1	0
No	18	17	22

Reporting group values	CHRONOS-B Arm 2 Focal + Finasteride	CHRONOS-B Arm 3 Focal + Bicalutamide	Total
Number of subjects	21	21	100

Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
log mean	65.71	66.52	
standard deviation	± 6.80	± 7.53	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	21	21	100
Ethnicity – n (%)			
Ethnicity – n (%)			
Units: Subjects			
White	15	17	67
Mixed	0	0	1
Asian	0	1	2
Black	1	1	3
Other	0	0	2
Not Reported	5	2	25
IMD Decile – n (%)			
Units: Subjects			
Decile 1	0	2	2
Decile 2	1	0	4
Decile 3	1	0	4
Decile 4	6	3	16
Decile 5	4	3	15
Decile 6	0	1	8
Decile 7	3	2	12
Decile 8	3	4	16
Decile 9	2	2	12
Decile 10	1	4	11
Digital Rectal Examination – n (%)			
Units: Subjects			
Normal findings	3	6	21
Abnormal findings	4	2	16
No	14	13	62
Missing from eCRF	0	0	1
Current medications			
Units: Subjects			
Yes	12	15	63
No	9	6	32

Missing from eCRF	0	0	5
5 alpha-reductase inhibitor2			
Units: Subjects			
Yes over (or equal to) 6 months ago	0	1	1
Yes within 6 months	0	0	1
No	21	20	93
Missing from eCRF	0	0	5
Tumour grade			
Units: Subjects			
Gleason 3+3	0	2	6
Gleason 3+4	17	16	76
Gleason 4+3	4	3	18
Local stage			
Units: Subjects			
Clinical T2/Radiological stage <T3a	18	19	93
Radiological T3a	3	2	7
Previous or current 5ARI use?			
Units: Subjects			
Yes	0	0	1
No	21	21	99

Subject analysis sets

Subject analysis set title	CHRONOS-A
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who took part in CHRONOS-A	
Subject analysis set title	CHRONOS-B
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who took part in CHRONOS-B	

Reporting group values	CHRONOS-A	CHRONOS-B	
Number of subjects	37	64	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
log mean			
standard deviation	±	±	

Gender categorical			
Units: Subjects			
Female	0	0	
Male	37	64	
Ethnicity – n (%)			
Ethnicity – n (%)			
Units: Subjects			
White	21	46	
Mixed	0	1	
Asian	1	1	
Black	0	3	
Other	1	1	
Not Reported	13	12	
IMD Decile – n (%)			
Units: Subjects			
Decile 1	0	2	
Decile 2	1	3	
Decile 3	2	2	
Decile 4	3	13	
Decile 5	4	11	
Decile 6	4	4	
Decile 7	6	6	
Decile 8	7	9	
Decile 9	4	8	
Decile 10	5	6	
Digital Rectal Examination – n (%)			
Units: Subjects			
Normal findings	8	13	
Abnormal findings	7	9	
No	20	42	
Missing from eCRF	1	0	
Current medications			
Units: Subjects			
Yes	23	40	
No	8	24	
Missing from eCRF	5	0	
5 alpha-reductase inhibitor2			
Units: Subjects			
Yes over (or equal to) 6 months ago	0	1	
Yes within 6 months	1	0	
No	30	63	
Missing from eCRF	5	0	
Tumour grade			
Units: Subjects			
Gleason 3+3	2	4	
Gleason 3+4	27	49	
Gleason 4+3	7	11	
Local stage			
Units: Subjects			
Clinical T2/Radiological stage <T3a	36	57	
Radiological T3a	0	7	

Previous or current 5ARI use?			
Units: Subjects			
Yes	1	0	
No	35	64	

End points

End points reporting groups

Reporting group title	CHRONOS-A Arm1 - Radical therapy
Reporting group description: Radical therapy (prostatectomy or radiotherapy [external beam or brachytherapy]). The type of radical therapy will be determined by physician or patient preference.	
Reporting group title	CHRONOS-A Arm 2 Focal Therapy
Reporting group description: Focal therapy alone (high intensity focused ultrasound [HIFU] or cryotherapy or other validated energy modality as per physician/patient decision/choice).	
Reporting group title	CHRONOS-B Arm 1 Focal Therapy
Reporting group description: Focal therapy alone (high intensity focused ultrasound [HIFU] or cryotherapy or other validated energy modality as per physician and centre choice).	
Reporting group title	CHRONOS-B Arm 2 Focal + Finasteride
Reporting group description: Neoadjuvant finasteride 5mg once daily for a minimum of 12 weeks (84 days) followed by focal therapy (as per control arm).	
Reporting group title	CHRONOS-B Arm 3 Focal + Bicalutamide
Reporting group description: Neoadjuvant bicalutamide 50mg once daily therapy for 12 weeks (84 days) followed by focal therapy (as per control arm).	
Subject analysis set title	CHRONOS-A
Subject analysis set type	Full analysis
Subject analysis set description: Subjects who took part in CHRONOS-A	
Subject analysis set title	CHRONOS-B
Subject analysis set type	Full analysis
Subject analysis set description: Subjects who took part in CHRONOS-B	

Primary: Mean number of patients recruited per month per centre

End point title	Mean number of patients recruited per month per centre ^[1]
End point description:	
End point type	Primary
End point timeframe: 12 months	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The Study was a Pilot, therefore there was no statistical analysis as the objectives were to determine patient acceptance to the Study and randomisation arms.

End point values	CHRONOS-A	CHRONOS-B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: Number of Subjects				
Charing Cross Hospital	4	32		
University Hospital Southampton NHS Foundation Tru	19	22		
Sunderland Royal Hospital	4	2		

Ashford & St Peter's Hospitals (ASPH) NHS Foundati	0	6		
Royal Marsden Hospital NHS Foundation Trust	2	0		
Hampshire Hospital NHS Foundation Trust	1	0		
Kingston Hospital NHS Foundation Trust	0	1		
West Middlesex University Hospital	5	1		
The Newcastle Upon Tyne Hospitals NHS Foundation T	2	0		
King's College Hospital NHS Foundation Trust	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Mean number of patients randomised per month per centre

End point title	Mean number of patients randomised per month per centre ^[2]
-----------------	--

End point description:

End point type	Primary
----------------	---------

End point timeframe:

12 months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The Study was a Pilot, therefore there was no statistical analysis as the objectives were to determine patient acceptance to randomisation, measured using rates of accrual and compliance, to CHRONOS-A & CHRONOS-B

End point values	CHRONOS-A	CHRONOS-B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	64		
Units: Number of Subjects				
Charing Cross Hospital	4	32		
University Hospital Southampton NHS Foundation Tru	19	22		
Sunderland Royal Hospital	4	2		
Ashford & St Peter's Hospitals (ASPH) NHS Foundati	0	6		
Royal Marsden Hospital NHS Foundation Trust	2	0		
Hampshire Hospital NHS Foundation Trust	1	0		
Kingston Hospital NHS Foundation Trust	0	1		
West Middlesex University Hospital	5	1		
The Newcastle Upon Tyne Hospitals NHS Foundation T	1	0		
King's College Hospital NHS Foundation Trust	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Recruitment rate

End point title	Recruitment rate ^[3]
-----------------	---------------------------------

End point description:

Number of Subjects recruited (consented) over total number of Subjects approached

End point type	Primary
----------------	---------

End point timeframe:

12 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The Study was a Pilot, therefore there was no statistical analysis as the objectives were to determine patient acceptance to randomisation, measured using rates of accrual and compliance, to CHRONOS-A & CHRONOS-B

End point values	CHRONOS-A	CHRONOS-B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	211	37		
Units: Percentage of Subjects				
number (confidence interval 95%)	17.5 (12.7 to 23.4)	43.2 (35.1 to 51.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Randomisation rates

End point title	Randomisation rates ^[4]
-----------------	------------------------------------

End point description:

The number of randomised patients over total number of patients recruited (consented)

End point type	Primary
----------------	---------

End point timeframe:

12 months

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The Study was a Pilot, therefore there was no statistical analysis as the objectives were to determine patient acceptance to randomisation, measured using rates of accrual and compliance, to CHRONOS-A & CHRONOS-B

End point values	CHRONOS-A	CHRONOS-B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36 ^[5]	64		
Units: Percentage of Subjects				
number (confidence interval 95%)	97.3 (85.8 to 99.9)	100 (94.4 to 100)		

Notes:

[5] - 1 patient withdrew

Statistical analyses

No statistical analyses for this end point

Primary: Treatment compliance

End point title	Treatment compliance ^[6]
-----------------	-------------------------------------

End point description:

End point type	Primary
----------------	---------

End point timeframe:

12 months

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The Study was a Pilot, therefore there was no statistical analysis as the objectives were to determine patient acceptance to randomisation, measured using rates of accrual and compliance, to CHRONOS-A & CHRONOS-B

End point values	CHRONOS-A Arm1 - Radical therapy	CHRONOS-A Arm 2 Focal Therapy	CHRONOS-B Arm 1 Focal Therapy	CHRONOS-B Arm 2 Focal + Finasteride
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	22	21
Units: Participants				
number (not applicable)				
Underwent treatment	13	16	22	21
Withdrawal	4	0	0	0
Screening failure	0	1	0	0

End point values	CHRONOS-B Arm 3 Focal + Bicalutamide			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Participants				
number (not applicable)				
Underwent treatment	21			
Withdrawal	0			
Screening failure	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

15 months

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	CTCAE
-----------------	-------

Dictionary version	4.0
--------------------	-----

Reporting groups

Reporting group title	CHRONOS-A
-----------------------	-----------

Reporting group description:

All subjects

Reporting group title	CHRONOS-B
-----------------------	-----------

Reporting group description: -

Serious adverse events	CHRONOS-A	CHRONOS-B	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 36 (5.56%)	6 / 64 (9.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Pleuritic chest pain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Torsades de Pointes			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Iatrogenic scrotal oedema (Primary)			

subjects affected / exposed	1 / 36 (2.78%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Urinary retention			
subjects affected / exposed	1 / 36 (2.78%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraphimosis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
urosepsis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visible haematuria			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
common bile duct stones	Additional description: caused infection		
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial Cellulitis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain	Additional description: Found to have E. coli in urine microbiology and blood cultures which caused the abdominal pain		
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	CHRONOS-A	CHRONOS-B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 36 (22.22%)	40 / 64 (62.50%)	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Cardiac disorders			
Pleuritic Chest Pain - Bilateral pulmonary emboli on CT imaging			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
stroke			
subjects affected / exposed	1 / 36 (2.78%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Torsades de Pointes			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
pancytopenia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Dry ongoing cough, Chest xray clear			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Knee Replacement			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Nocturia			

subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 64 (1.56%) 1	
Painful nipples subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 64 (1.56%) 1	
Nausea and Vomiting subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 64 (1.56%) 1	
Worsening night sweats subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 64 (1.56%) 1	
Immune system disorders			
Allergic reaction to excipient subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 64 (1.56%) 1	
COVID-19 subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	0 / 64 (0.00%) 0	
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	1 / 64 (1.56%) 1	
Constipation subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 64 (1.56%) 1	
Psychiatric disorders			
Depression subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 64 (1.56%) 1	
Post traumatic stress disorder subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 64 (1.56%) 1	
Short term memory loss subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 64 (1.56%) 1	
Renal and urinary disorders			

Blood from urethral meatus when straining		
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	1
Dry Orgasm		
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	1
Ejaculatory dysfunction		
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	1
Elective (planned) parathyroidectomy		
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	1
Epididymo-orchitis		
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	1
Erectile Dysfunction		
subjects affected / exposed	0 / 36 (0.00%)	15 / 64 (23.44%)
occurrences (all)	0	15
Failed removal of common bile duct stones		
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	1
Haematuria		
subjects affected / exposed	1 / 36 (2.78%)	2 / 64 (3.13%)
occurrences (all)	1	2
Haematospermia		
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	1
Iatrogenic Scrotal Oedema		
subjects affected / exposed	1 / 36 (2.78%)	0 / 64 (0.00%)
occurrences (all)	1	0
Low urinary flow rate		
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	1
Lower Urinary Tract Symptoms		

subjects affected / exposed	0 / 36 (0.00%)	4 / 64 (6.25%)	
occurrences (all)	0	4	
Painless swelling and mild bruising of scrotal and penile skin			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Paraphimosis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
patient required TURP after urosepsis and retention			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Penile numbness			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Penile tip pain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Prostate Inflammation	Additional description: Post HIFU Prostate Inflammation		
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Prostatitis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Rectal fissure			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Removal of stones from common bile duct			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Severe LUTS			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Suspected common bile duct stone/pancreatitis,	Additional description: serum amylase raised		

subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Sweaty testicles			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Swollen testicles			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Urgency of micturition			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Urinary Retention			
subjects affected / exposed	1 / 36 (2.78%)	5 / 64 (7.81%)	
occurrences (all)	1	5	
Urine leaking around catheter	Additional description: catheter blocked, requires flushing.		
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Visible haematuria			
subjects affected / exposed	0 / 36 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Infections and infestations			
Bacterial Cellulitis and Related Conditions			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Campylobacter			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Chest infection			
subjects affected / exposed	1 / 36 (2.78%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Complications of urinary catheter			
subjects affected / exposed	0 / 36 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Infection following tooth extraction			

subjects affected / exposed	1 / 36 (2.78%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 36 (2.78%)	12 / 64 (18.75%)	
occurrences (all)	1	12	
UTI, epididymo-orchitis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 64 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 October 2019	<p>Strata update as with the current number of strata, as a combination, would lead to small groups of patients in certain categories, that would not be able to be used for useful analysis.</p> <ul style="list-style-type: none">• Removal or repeating sections in the trial summary boxes• One inclusion criterion has been moved to the treatment arm paragraph as it was not an inclusion criterion but rather a prompt.• Mention of partial postcode has been updated to postcode as this will be required to calculate the Index of Deprivation.• Mention of expected SAEs included within the Protocol for clarification
11 November 2019	<p>The following changes included:</p> <ul style="list-style-type: none">• Radiation risk calculations in the IRAS form (Part B, section 3 A1)• Discussion regarding standard of care scans (Part A, A22)• Addition of standard of care scans and treatment option of brachytherapy (Part A, A19)• Maximum radiation dose of patients enrolled into CHRONOS (Part B, A2)• Radiation dose for individual investigations and treatments (Part B, B1)• Additional information regarding total dose of radiation treatment (Part C, C1)• Change in MPE (Part C, C3)• Change in CRE (Part D, D4)• CHRONOS A & B PIS includes information regarding radiation risks• CHRONOS A & B ICFs reflect new version of PIS• Addition of companion PIS and ICF for optional audio-recording• For clarity the definition of brachytherapy biochemical failure and brachytherapy treatment failure have been outlined and the definition of treatment failure in CHRONOS A focal therapy arm has also been clarified within the Protocol.
27 January 2020	<p>Hampshire Hospital NHS Foundation Trust – The PI has been updated from Amr Emara to Richard Hindley due to other work commitments.</p> <p>- Frimley Health NHS Foundation Trust :</p> <ul style="list-style-type: none">o Wexham Park Hospital – This new site has been added to the study. Jeetesh Bhardwa will be the PI.o Frimley Park Hospital - The PI has been updated from Jeetesh Bhardwa to the new principle investigator Simon Bott
03 March 2020	<p>addition of a new site to the Study:</p> <ul style="list-style-type: none">- Chelsea & Westminster NHS Foundation Trust – The PI will be Mathias Winkler
05 November 2020	<p>Addition of the site King's College Hospital NHS Foundation Trust. The PI will be Professor Gordon Muir.</p> <p>Removal of reference to contact the Study Clinical Manager Dr Deepika Reddy in the following PIS documents due to change of staff arrangements.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 March 2020	COVID-19 arose, whereby the UK was placed in lockdown and many sites were either paused for a short while or treatment times were delayed.	-

Notes:

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32302790>