Internal Pilot Results: Tables to Present

Report Date: 27/01/2023

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

IP4 - CHRONOS

19CX5006

Study Investigators:

Chief Investigator: Prof. Hashim Uddin Ahmed

Study Management: Imperial Clinical Trials Unit (ICTU)

All tables presented are taken from SAP v1.0

This document should be read in conjunction with SAP v1.0

Document prepared by Consuelo Nohpal de la Rosa (Trial Statistician)

Signed by:	**Role**	**Signature**
Dr Francesca Fiorentino	Senior Statistician	Francesca Fiorentino (k2145850) Digitally signed by Francesca Fiorentino (k2145850) Date: 2023.02.02 16:59:49 Z
Consuelo Nohpal de la Rosa	Study Statistician	Consuelo Nohpal de la Rosa Digitally signed by Consuelo Nohpal de la Rosa Date: 2023.02.02 19:08:07 Z

Contents

1. Study Population

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

2. Summary of Study Treatments and Procedures

2.1. CHRONOS-A

CHRONOS-A was a two arm RCT.

• Arm 1 (Control): Radical therapy (radiotherapy or prostatectomy [radiotherapy can be external beam or brachytherapy]). In patients undergoing radiotherapy, a maximum of 6-months neo-adjuvant hormonal therapy was allowed. In patients undergoing radical prostatectomy, cytoreduction a maximum of 6 months with medication was permissible, provided this was part of local practice.

• Arm 2 (Intervention): Focal therapy alone (high intensity focused ultrasound [HIFU] or cryotherapy as per physician and centre choice). A second focal therapy session in-field, or a first focal therapy session to an out-of-field progressive or de novo lesion was allowed as part of the focal therapy intervention.

2.2. CHRONOS-B

CHRONOS-B was a Multi-Arm Multi-Stage (MAMS) RCT.

• Arm 1 (Control): Focal therapy alone (high intensity focused ultrasound [HIFU] or cryotherapy as per physician and centre choice). A second treatment in-field, or a first focal ablation to an out-of-field progressive or de novo lesion was allowed but were regarded as failure events for the purpose of CHRONOS-B.

• Arm 2 (Intervention): Neoadjuvant finasteride 5mg once daily for a minimum of 12 weeks followed by focal therapy (as per control arm).

• Arm 3 (Intervention): Neoadjuvant bicalutamide 50mg once daily therapy for a minimum of 12 weeks followed by focal therapy (as per control arm).

3. Sample Size

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

- CHRONOS-A: At a conservative rate the two-arm RCT was expected to recruit 60 patients in the Pilot Stage in 6 centres over 12-months. It reached its recruitment target in December 2021. The final number of recruited patients was 64.
- CHRONOS-B: The three-arm MAMS RCT was expected to recruit 60 patients in the Pilot Stage in 6 centres over 12-months. CHRONOS B did not reach the expected target of 60 as the study closed recruitment on the 30th of April 2022. The final number of patients recruited was 37.

4. Analysis Set

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

5. Working Definitions

5.1. Definition of Recruitment rate

Recruitment rate is calculated as the number of participants recruited (consented) out of the total number approached.

5.2. Definition of Randomisation rate

Randomisation rate is calculated as the number of participants randomised out of the total number recruited (consented).

5.3. Definition of Compliance

Compliance comprises both 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 is 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).

6. PROMS Scoring

6.1. 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 (1):

- 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".

6.2. 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 (2).

6.3. 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" (2). 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.

6.4. 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 (3).

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 (3).

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

6.5. 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 (4). 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 (4):

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 (4).

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

6.6. 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 (4). 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 (4):

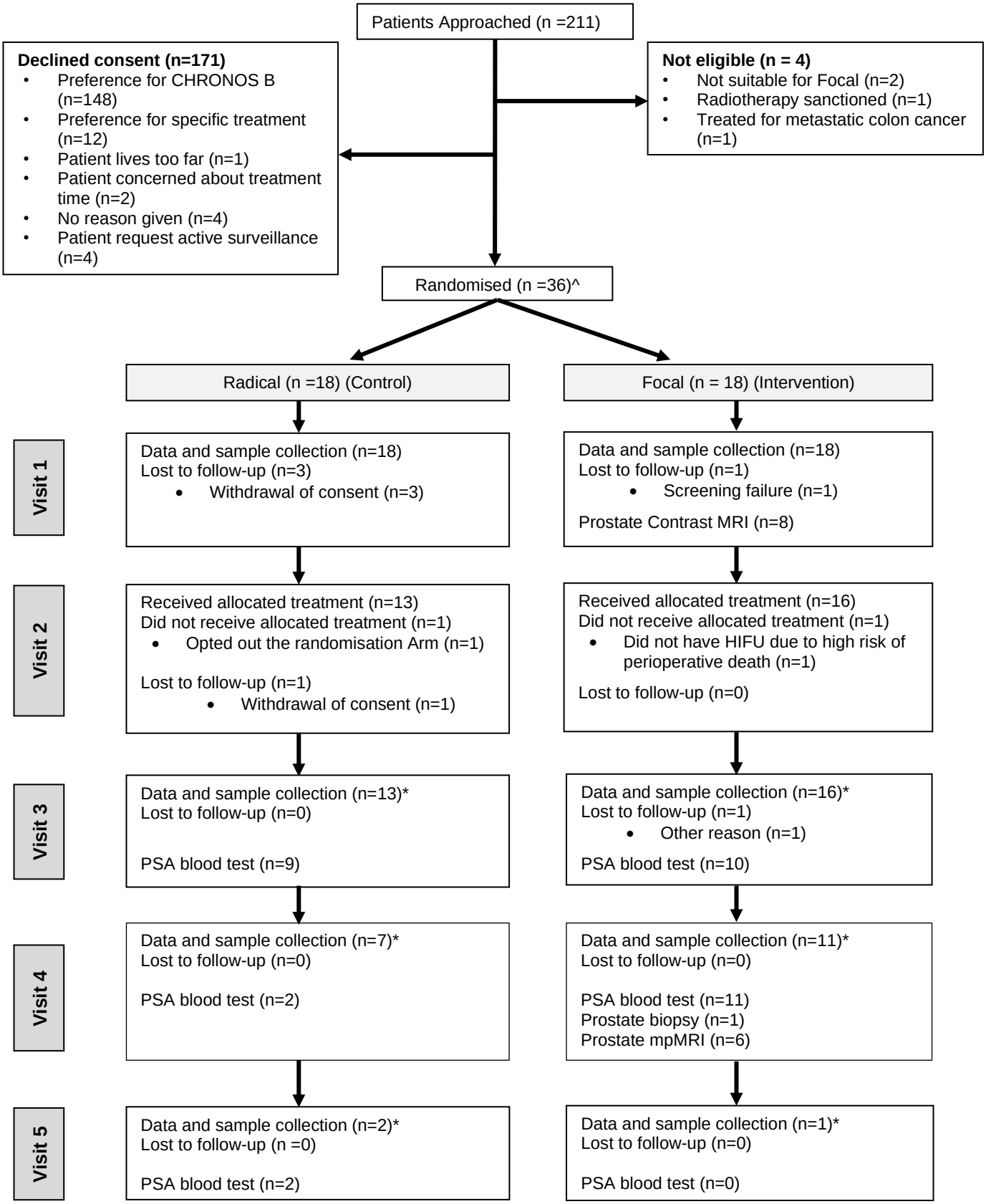
Question Number	Item Number	Item Response Value	Standardised Value
1, 2, 3	23, 24, 25	1 2 3 4 5	0 25 50 75 100
4	26	1 2 3 4	0 33 67 100
5	27	0 1 2 3	100 67 33 0
6a, 6b, 6c, 6d, 6e, 6f	28, 29, 30, 31, 32, 33	0 1 2 3 4	100 75 50 25 0
7	34	1 2 3 4 5	100 75 50 25 0

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 (4).

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
Urinary Summary	1,2,3,4,5, 6a, 6b, 6c, 6d, 6e, 6f, 7	23-34	10

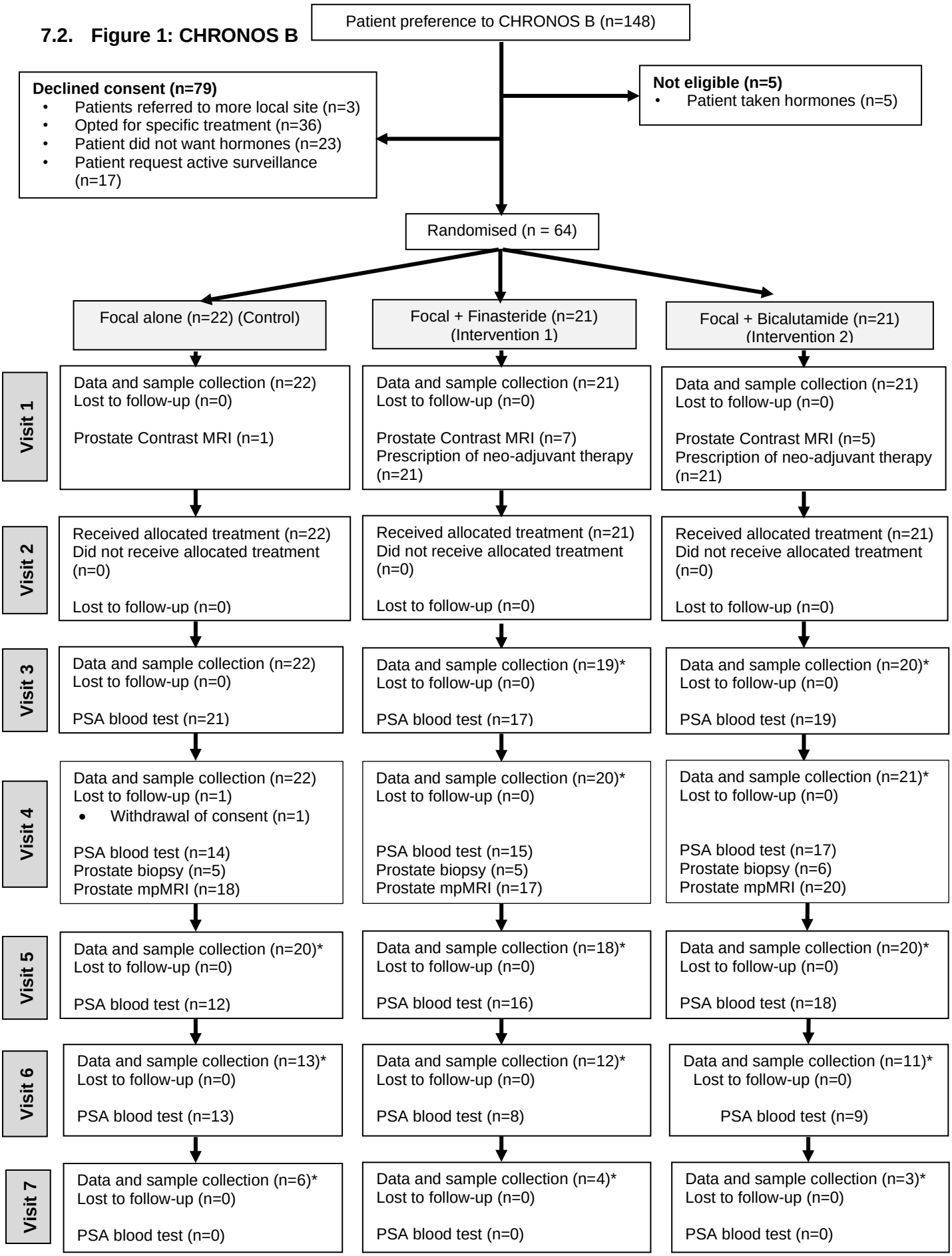
7. Internal Pilot: CONSORT Diagrams

7.1. Figure 1: CHRONOS A



^ There were 37 patients who consented, but before randomisation one patient was identified as a screening failure, so the patient was classified as not eligible.
*Some patients have not reached the visit time during the trial yet.

7.2. Figure 1: CHRONOS B



*Patients have not reached the visit time during the trial yet

8. Tables to present

8.1. Baseline Characteristics

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

Variable	Statistics	Focal	Radical	Total
Age	N	18	18	36
	Mean (SD)	69.28 (4.60)	68.78 (7.64)	69.03 (6.22)
	Median (IQR)	69.50 (67.00-72.00)	68.00 (62.00-74.00)	69.00 (66.00-72.00)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity – n (%)	N	18	18	36
	White	13 (72.2%)	8 (44.4%)	21 (58.3%)
	Mixed	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	0 (0.0%)	1 (5.6%)	1 (2.8%)
	Black	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	0 (0.0%)	1 (5.6%)	1 (2.8%)
	Not Reported	5 (27.8%)	8 (44.4%)	13 (36.1%)
IMD Decile – n (%)	N	18	18	36
	1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	2	1 (5.6%)	0 (0.0%)	1 (2.8%)
	3	1 (5.6%)	1 (5.6%)	2 (5.6%)
	4	1 (5.6%)	2 (11.1%)	3 (8.3%)
	5	2 (11.1%)	2 (11.1%)	4 (11.1%)
	6	2 (11.1%)	2 (11.1%)	4 (11.1%)
	7	4 (22.2%)	2 (11.1%)	6 (16.7%)
	8	4 (22.2%)	3 (16.7%)	7 (19.4%)
	9	1 (5.6%)	3 (16.7%)	4 (11.1%)
	10	2 (11.1%)	3 (16.7%)	5 (13.9%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Digital Rectal Examination – n (%)	N	18	18	36
	Yes:	9 (50.0%)	6 (33.3%)	15 (41.7%)
	Normal findings[1]	5 (27.8%)	3 (16.7%)	8 (22.2%)
	Abnormal findings[1]	4 (22.2%)	3 (16.7%)	7 (19.4%)
		0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	8 (44.4%)	12 (66.7%)	20 (55.6%)
	Missing from eCRF – n (%)	1 (5.6%)	0 (0.0%)	1 (2.8%)
Current medications – n (%)	N	18	18	36
	Yes	12 (66.7%)	11 (61.1%)	23 (63.9%)
	No	3 (16.7%)	5 (27.8%)	8 (22.2%)
	Missing from eCRF – n (%)	3 (16.7%)	2 (11.1%)	5 (13.9%)
5 alpha-reductase inhibitor[2] – n (%)	N	18	18	36
	Yes over (or equal to) 6 months ago	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Yes within 6 months	1 (5.6%)	0 (0.0%)	1 (2.8%)
	No	14 (77.8%)	16 (88.9%)	30 (83.3%)
	Missing from eCRF – n (%)	3 (16.7%)	2 (11.1%)	5 (13.9%)
Stratification Factors				
Tumour grade (n (%))	Gleason 3+3	1 (5.6%)	1 (5.6%)	2 (5.6%)
	Gleason 3+4	13 (72.2%)	14 (77.8%)	27 (75.0%)
	Gleason 4+3	4 (22.2%)	3 (16.7%)	7 (19.4%)
Local stage (n (%))	Clinical T2/Radiological stage <T3a	18 (100.0%)	18 (100.0%)	36 (100.0%)
	Radiological T3a	0 (0.0%)	0 (0.0%)	0 (0.0%)
Previous or current 5ARI use? (n (%))	Yes	1 (5.6%)	0 (0.0%)	1 (2.8%)
	No	17 (94.4%)	18 (100.0%)	35 (97.2%)

[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 N=18	Radical N=18	Total N=36
Severity – n (%)	N	13	8	21
	Mild = ≤ 7	4 (22.2%)	3 (16.7%)	7 (19.4%)
	Moderate = 8-19	6 (33.3%)	3 (16.7%)	9 (25.0%)
	Severe = 20-35	3 (16.7%)	2 (11.1%)	5 (13.9%)
	Missing from eCRF – n (%)	5 (27.8%)	10 (55.6%)	15 (41.7%)
Summary statistics	N	13	8	21
	Mean (SD)	12.15 (7.69)	12.00 (7.89)	12.10 (7.57)
	Median (IQR)	12.00 (5.00-17.00)	10.50 (5.00-19.00)	11.00 (5.00-17.00)
	Missing from eCRF – n (%)	5 (27.8%)	10 (55.6%)	15 (41.7%)

[1]See section 6.1 for details

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

Variable	Statistics	Focal N=18	Radical N=18	Total N=36
MCCL	N	17	18	35
	Mean (SD)	7.59 (2.98)	6.67 (2.40)	7.11 (2.70)
	Median (IQR)	8.00 (7.00-9.00)	7.00 (5.00-8.00)	7.00 (5.00-9.00)
	Missing from eCRF – n (%)	1 (5.6%)	0 (0%)	1 (2.8%)

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

Gleason Grade	Statistics	MCCL (N=36)
3+3	N	N=2
	Mean (SD)	8.00 (1.41)
	Median (IQR)	8.00 (7.00-9.00)
	Missing from eCRF – n (%)	0 (0%)
3+4	N	N=25
	Mean (SD)	6.64 (2.58)
	Median (IQR)	7.00 (5.00-9.00)
	Missing from eCRF – n (%)	0 (0%)
3+5	N	N=0
	Mean (SD)	0 (0.0%)
	Median (IQR)	0 (0.0%)
	Missing from eCRF – n (%)	0 (0.0%)
4+3	N	N=8
	Mean (SD)	8.38 (3.07)
	Median (IQR)	8.00 (6.00-10.00)
	Missing from eCRF – n (%)	0 (0.0%)
4+4	N	N=0
	Mean (SD)	0 (0.0%)
	Median (IQR)	0 (0.0%)
	Missing from eCRF – n (%)	0 (0.0%)
4+5	N	N=0
	Mean (SD)	0 (0.0%)
	Median (IQR)	0 (0.0%)
	Missing from eCRF – n (%)	0 (0.0%)
5+3	N	N=0
	Mean (SD)	0 (0.0%)
	Median (IQR)	0 (0.0%)
	Missing from eCRF – n (%)	0 (0.0%)
5+4	N	N=0
	Mean (SD)	0 (0.0%)
	Median (IQR)	0 (0.0%)
	Missing from eCRF – n (%)	0 (0.0%)
5+5	N	N=0
	Mean (SD)	0 (0.0%)
	Median (IQR)	0 (0.0%)
	Missing from eCRF – n (%)	0 (0.0%)
Total	N	N=35
	Mean (SD)	7.11 (2.70)
	Median (IQR)	7.00 (5.00-9.00)
	Missing from eCRF – n (%)	1* (2.8%)

*One patient had missing information in both measurement of Gleason grade and MCCL

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

Variable	Statistics	Focal + finasteride	Focal + bicalutamide	Focal alone	Total
Age	N	21	21	22	64
	Mean (SD)	65.71 (6.80)	66.52 (7.53)	64.55 (7.00)	65.58 (7.05)
	Median (IQR)	67.00 (63.00-69.00)	65.00 (61.00-72.00)	65.00 (59.00-71.00)	66.00 (60.50-70.00)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity – n (%)	N	21	21	22	64
	White	15 (71.4%)	17 (81.0%)	14 (63.6%)	46 (71.9%)
	Mixed	0 (0.0%)	0 (0.0%)	1 (4.5%)	1 (1.6%)
	Asian	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (1.6%)
	Black	1 (4.8%)	1 (4.8%)	1 (4.5%)	3 (4.7%)
	Other	0 (0.0%)	0 (0.0%)	1 (4.5%)	1 (1.6%)
	Not Reported	5 (23.8%)	2 (9.5%)	5 (22.7%)	12 (18.8%)
IMD Decile – n (%)	N	21	21	22	64
	1	0 (0.0%)	2 (9.5%)	0 (0.0%)	2 (3.1%)
	2	1 (4.8%)	0 (0.0%)	2 (9.1%)	3 (4.7%)
	3	1 (4.8%)	0 (0.0%)	1 (4.5%)	2 (3.1%)
	4	6 (28.6%)	3 (14.3%)	4 (18.2%)	13 (20.3%)
	5	4 (19.0%)	3 (14.3%)	4 (18.2%)	11 (17.2%)
	6	0 (0.0%)	1 (4.8%)	3 (13.6%)	4 (6.3%)
	7	3 (14.3%)	2 (9.5%)	1 (4.5%)	6 (9.4%)
	8	3 (14.3%)	4 (19.0%)	2 (9.1%)	9 (14.1%)
	9	2 (9.5%)	2 (9.5%)	4 (18.2%)	8 (12.5%)
	10	1 (4.8%)	4 (19.0%)	1 (4.5%)	6 (9.4%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Digital Rectal Examination – n (%)	N	21	21	22	64
	Yes:	7 (33.3%)	8 (38.1%)	7 (31.8%)	22 (34.4%)
	Normal findings[1]	3 (14.3%)	6 (28.6%)	4 (18.2%)	13 (20.3%)
	Abnormal findings[1]	4 (19.0%)	2 (9.5%)	3 (13.6%)	9 (14.1%)
		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	14 (66.7%)	13 (61.9%)	15 (68.2%)	42 (65.6%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Current medications – n (%)	N	21	21	22	64
	Yes	12 (57.1%)	15 (71.4%)	13 (59.1%)	40 (62.5%)
	No	9 (42.9%)	6 (28.6%)	9 (40.9%)	24 (37.5%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5 alpha-reductase inhibitor[2] – n (%)	N	21	21	22	64
	Yes over (or equal to) 6 months ago	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (1.6%)
	Yes within 6 months	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	21 (100.0%)	20 (95.2%)	22 (100.0%)	63 (98.4%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stratification Factors					
Tumour grade (n (%))	Gleason 3+3	0 (0.0%)	2 (9.5%)	2 (9.1%)	4 (6.3%)
	Gleason 3+4	17 (81.0%)	16 (76.2%)	16 (72.7%)	49 (76.6%)
	Gleason 4+3	4 (19.0%)	3 (14.3%)	4 (18.2%)	11 (17.2%)
Local stage (n (%))	Clinical T2/Radiological stage <T3a	18 (85.7%)	19 (90.5%)	20 (90.9%)	57 (89.1%)
	Radiological T3a	3 (14.3%)	2 (9.5%)	2 (9.1%)	7 (10.9%)

[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 N=21	Focal + bicalutamide N=21	Focal alone N=22	Total N=64
Severity – n (%)	N	18	18	18	54
	Mild = ≤ 7	5 (23.8%)	5 (23.8%)	6 (27.3%)	16 (25.0%)
	Moderate = 8-19	11 (52.4%)	13 (61.9%)	10 (45.5%)	34 (53.1%)
	Severe = 20-35	2 (9.5%)	0 (0.0%)	2 (9.1%)	4 (6.3%)
	Missing from eCRF – n (%)	3 (14.3%)	3 (14.3%)	4 (18.2%)	10 (15.6%)
Summary statistics	N	18	18	18	54
	Mean (SD)	10.56 (7.72)	10.33 (5.70)	12.67 (8.42)	11.19 (7.31)
	Median (IQR)	10.00 (7.00-12.00)	10.00 (6.00-12.00)	11.00 (5.00-18.00)	10.00 (6.00-16.00)
	Missing from eCRF – n (%)	3 (14.3%)	3 (14.3%)	4 (18.2%)	10 (15.6%)

[1]See section 6.1 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 N=21	Focal + bicalutamide N=21	Focal alone N=22	Total N=64
MCCL	N	20	21	20	61
	Mean (SD)	6.55 (3.56)	7.00 (3.62)	7.15 (3.73)	6.90 (3.59)
	Median (IQR)	6.00 (3.50-9.50)	7.00 (5.00-10.00)	7.00 (4.00-10.00)	7.00 (4.00-10.00)
	Missing from eCRF – n (%)	1 (4.8%)	0 (0%)	2 (9.1%)	3 (4.7%)

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

Gleason Grade	Statistics	MCCL (N=64)
3+3	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	N=4 9.00 (1.73) 10.00 (7.00-10.00) 1 (25%)
3+4	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	N=47 6.89 (3.56) 7.00 (4.00-10.00) 2 (4.3%)
3+5	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	N=0 0 (0.0%) 0 (0.0%) 0 (0.0%)
4+3	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	N=13 6.46 (3.99) 5.00 (4.00-10.00) 0 (0.0%)
4+4	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	N=0 0 (0.0%) 0 (0.0%) 0 (0.0%)
4+5	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	N=0 0 (0.0%) 0 (0.0%) 0 (0.0%)
5+3	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	N=0 0 (0.0%) 0 (0.0%) 0 (0.0%)
5+4	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	N=0 0 (0.0%) 0 (0.0%) 0 (0.0%)
5+5	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	N=0 0 (0.0%) 0 (0.0%) 0 (0.0%)
Total	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	N=61 6.90 (3.59) 7.00 (4.00-10.00) 3* (4.7%)

*Three patients had missing information on MCCL measurement, but they did not have Gleason grade classification

8.2. Analysis of Primary End Points

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

CHRONOS-A	CHRONOS-B	Total
37 (36.6%)	64 (63.4%)	101 (100.0%)

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

	Centre	Number of patients		Period of recruitment[1] (months)	Mean number of patients per month[2]	
		Recruited	Randomised		Recruited	Randomised
CHRONOS-A	Charing Cross Hospital	4	4	24	0.17	0.17
	University Hospital Southampton NHS Foundation Trust	19	19	14	1.36	1.36
	Sunderland Royal Hospital	4	4	17	0.24	0.24
	Ashford & St Peter's Hospitals (ASPH) NHS Foundation Trust	0	0	23	0.00	0.00
	Royal Marsden Hospital NHS Foundation Trust	2	2	11	0.18	0.18
	Hampshire Hospital NHS Foundation Trust	1	1	6	0.17	0.17
	Kingston Hospital NHS Foundation Trust	0	0	12	0.00	0.00
	West Middlesex University Hospital	5	5	12	0.42	0.42
	The Newcastle Upon Tyne Hospitals NHS Foundation Trust	2	1	9	0.22	0.11
	King's College Hospital NHS Foundation Trust	0	0	6	0.00	0.00
	Total	**37**	**36**			
CHRONOS-B	Charing Cross Hospital	32	32	15	2.13	2.13
	University Hospital Southampton NHS Foundation Trust	22	22	14	1.57	1.57
	Sunderland Royal Hospital	2	2	8	0.25	0.25
	Ashford & St Peter's Hospitals (ASPH) NHS Foundation Trust	6	6	14	0.43	0.43
	Royal Marsden Hospital NHS Foundation Trust	0	0	4	0.00	0.00
	Kingston Hospital NHS Foundation Trust	1	1	3	0.33	0.33
	West Middlesex University Hospital	1	1	2	0.50	0.50
	Total	**64**	**64**			

[1]Period of recruitment in months was calculated using the date that the sites were open for recruitment till the date that the recruitment was closed (30/11/2021) for CHRONOS A and up to 28/02/2021 for CHRONOS B minus the pause period (only for site 3) due to the COVID-19 pandemic.
[2]Mean number of patients per month was obtained by dividing the number of patients per site by the time in months for the recruited and randomised patients.

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

	Recruitment Rate[1]	Randomisation Rate[2]
CHRONOS-A	17.5% (37/211)	97.3% (36/37)
95% CI	12.7% to 23.4%	85.8% to 99.9%
CHRONOS-B	43.2% (64/148)	100.0% (64/64)
95% CI	35.1% to 51.6%	94.4% to 1*

[1]Defined as number recruited (consented) over total number of patients approached.
[2]Defined as number of randomised patients over total number of patients recruited (consented)
(*) one-sided, 97.5% confidence interval

8.3. Figures to Present

- **Graph displaying recruitment rate over time (CHRONOS-A and CHRONOS-B)**

Since the calculation of the recruitment rate by month needs information on number of patients approached by month and this information was only collected by site, these graphs were omitted.

Figure 2: Graph displaying the cumulative number of patients recruited out of the Original Predicted target, the Adjusted and Actual target over time for (CHRONOS-A)

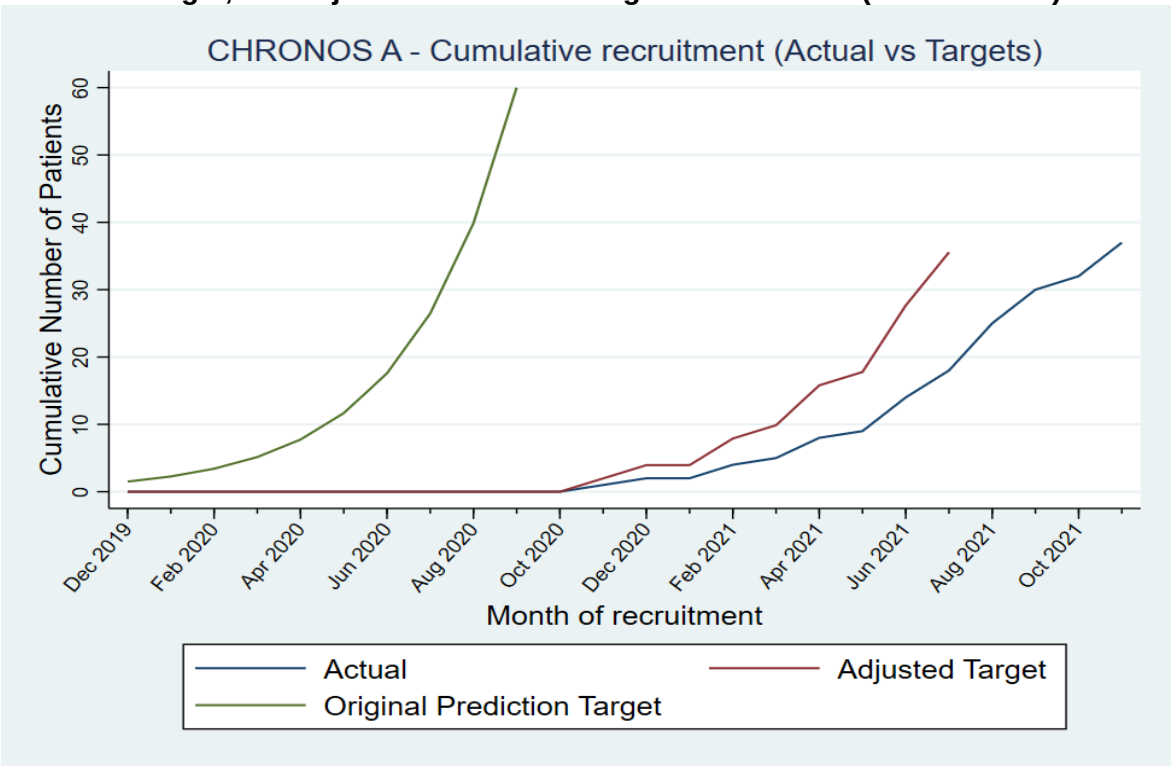


Figure 3: Graph displaying the cumulative number of patients recruited over time (actual vs target) (CHRONOS-B)

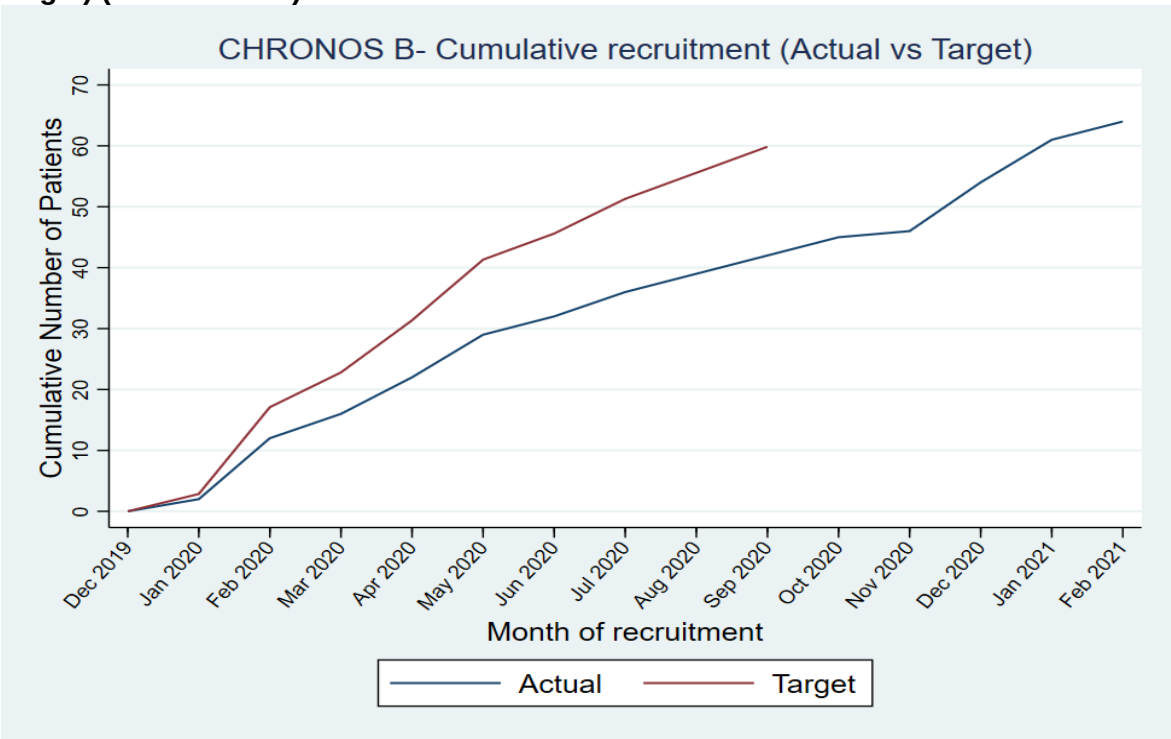


Figure 4: Graph displaying randomisation rate over time (CHRONOS-A)

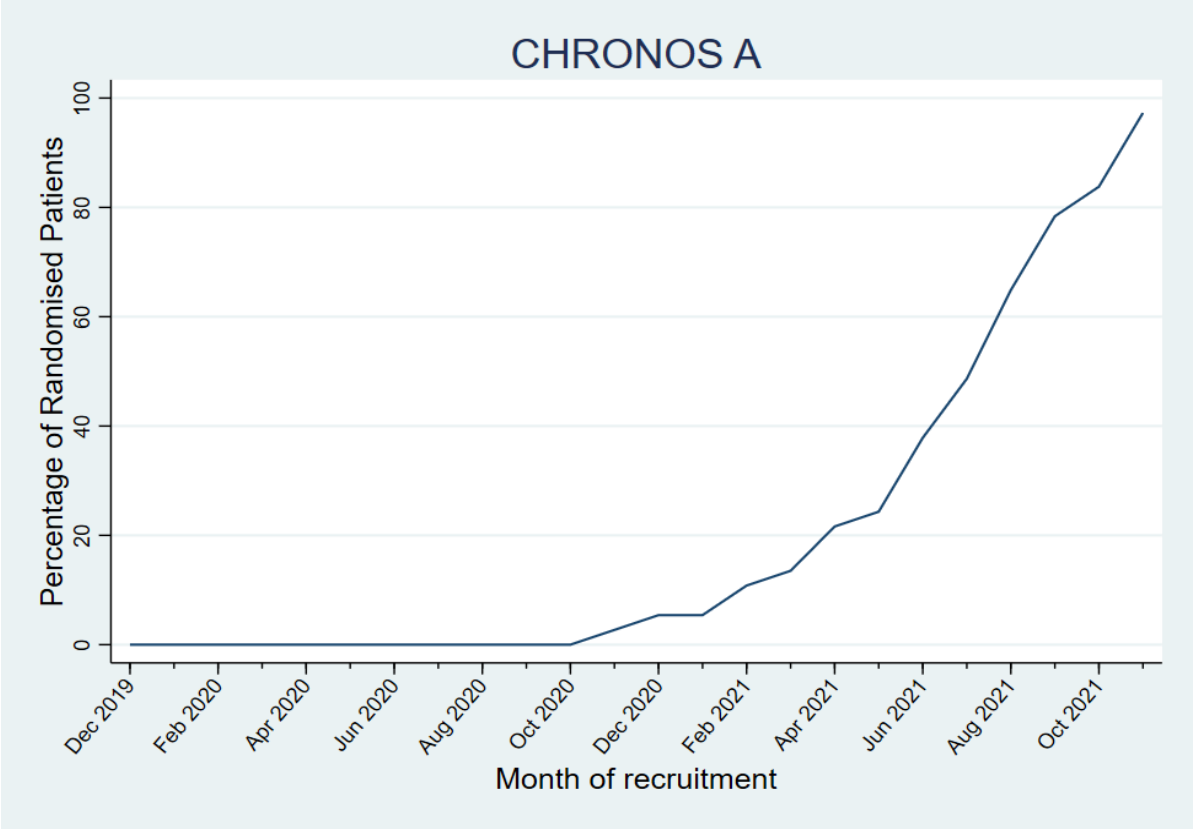


Figure 5: Graph displaying randomisation rate over time (CHRONOS-B)

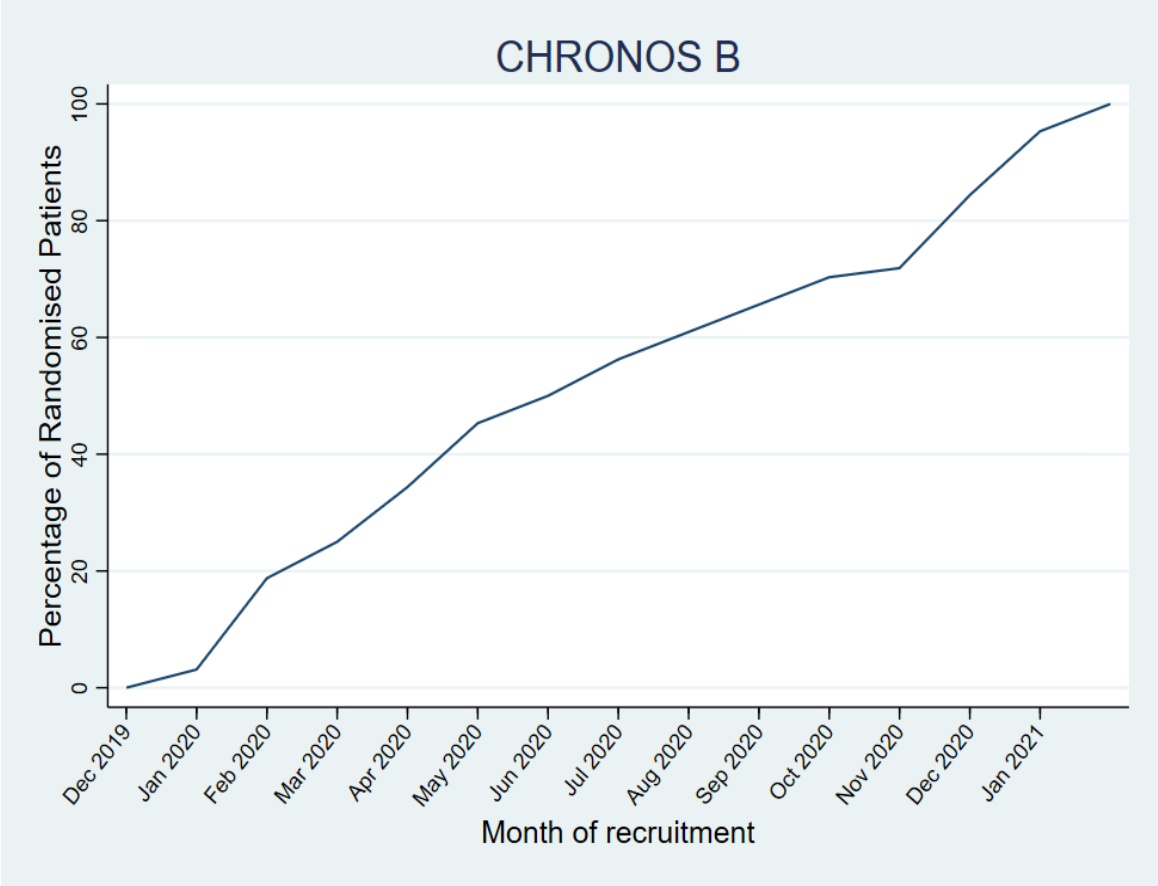


Figure 6: Graphs displaying Original and Adjusted Predictions and Actual Recruitment for CHRONOS A*

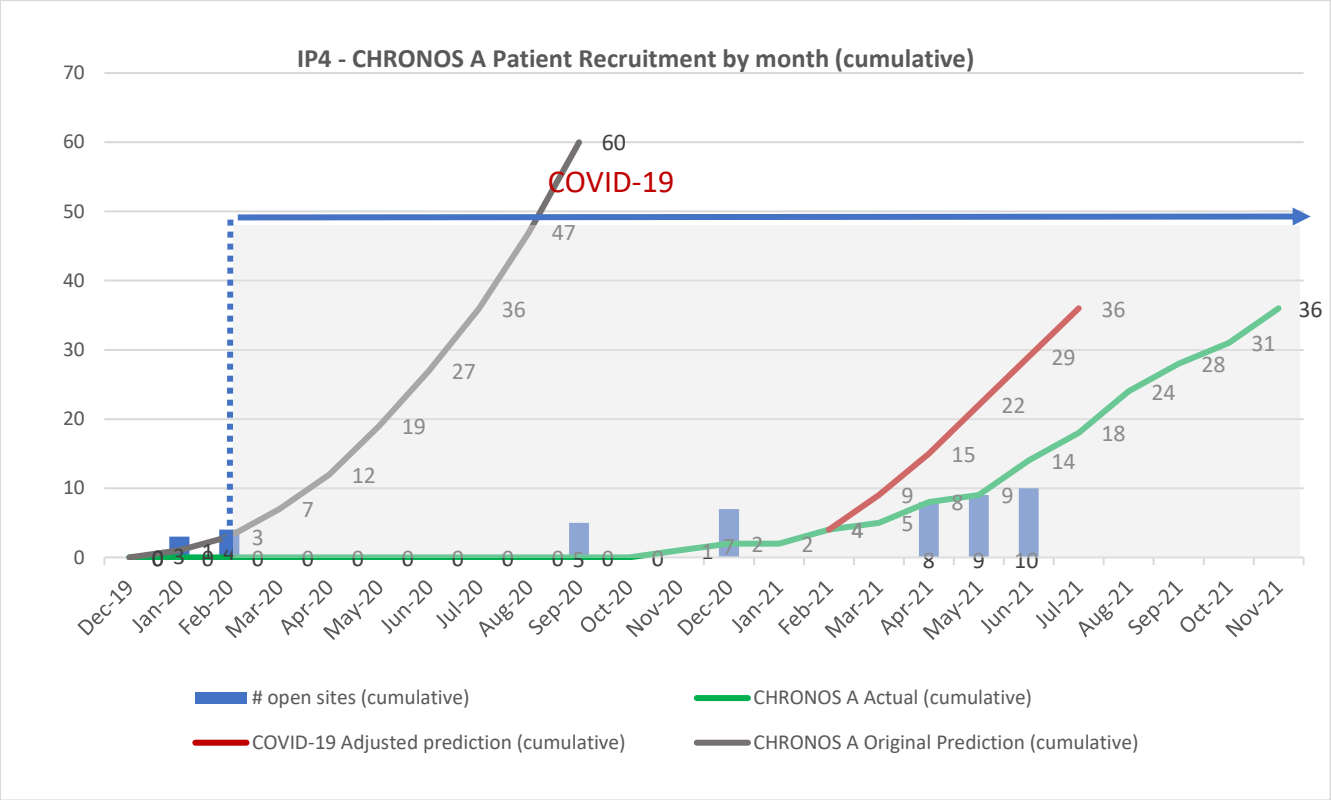


Figure 6 was added to the report as it was given by the trial manager. However, the figure was not created using the information from the database. Figure 2 uses the exact dates and information from the database.

Figure 7: Graphs displaying Original and Adjusted Predictions and Actual Recruitment for CHRONOS B

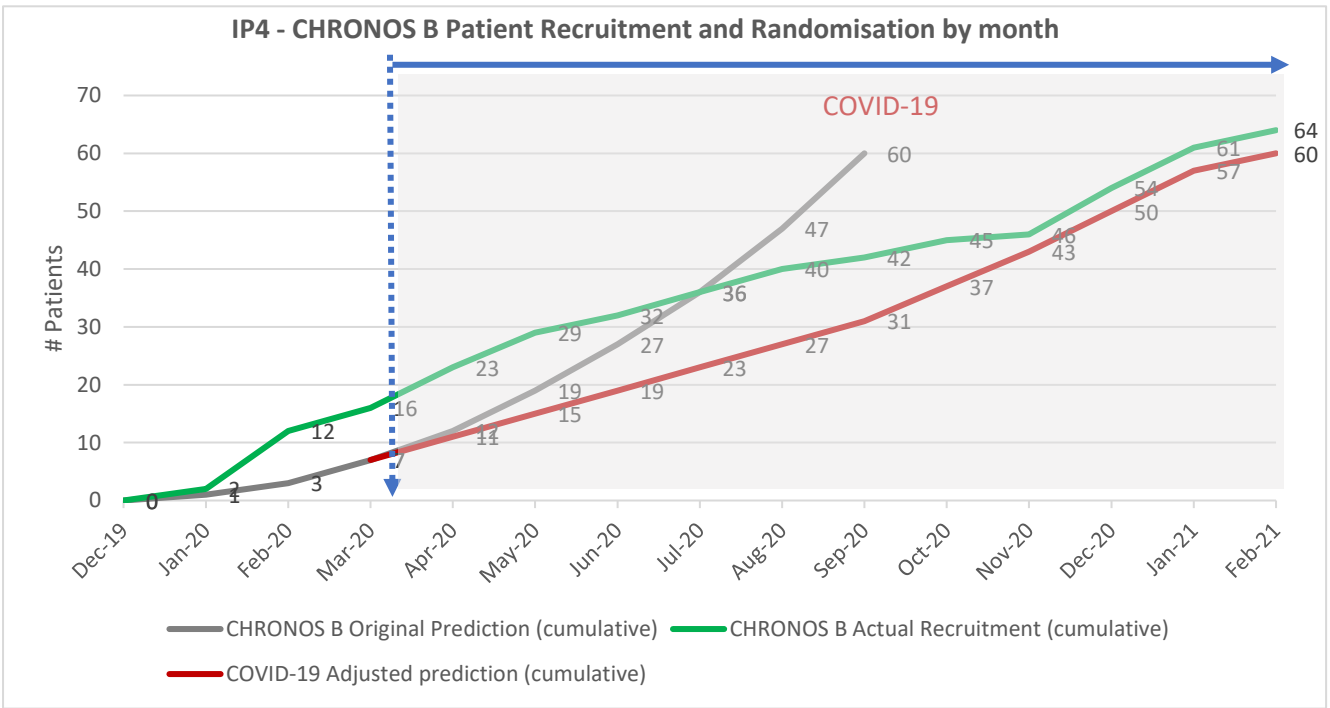


Figure 7 was added to the report as it was given by the trial manager. However, the figure was not created using the information from the database. Figure 2 uses the exact dates and information from the database.

Table A1: Summary of Recruitment and Randomisation by Site – CHRONOS-A

Site[1]	Date site opened		COVID - 19																							Total Number Recruited	Total Number Randomised
		2019	2020												2021												
		Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov		
CHR1	11/12/2019	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	2	0	1	4	4
CHR2	29/09/2020										0	0	1	1	0	1	1	0	0	4	2	5	1	1	2	19	19
CHR3	29/02/2020			0	X[2]	X[2]	X[2]	X[2]	0	0	0	0	0	0	0	0	0	0	0	0	2	1	1	0	0	4	4
CHR4	09/01/2020		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CHR5	14/01/2021														0	0	0	0	0	0	0	0	0	1	1	2	2
CHR8	20/05/2021				X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]							0	0	0	0	0	0	1	1	1
CHR10	11/12/2020				X[2]	X[2]	X[2]	X[2]	X[2]	X[2]				0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CHR11	14/12/2020													0	0	1	0	3	0	0	0	0	1	0	0	5	5
CHR12	08/03/2021				X[2]	X[2]	X[2]	X[2]	X[2]	X[2]							0	0	1	0	0	1	0	0	0	2	1
CHR16	09/06/2021																			0	0	0	0	0	0	0	0
Total		0	0	0	0	0	0	0	0	0	0	0	1	1	0	2	1	3	1	5	4	6	5	2	5	37	36

[1]Site Mnemonic:

CHR1 - Charing Cross Hospital
CHR2 - University Hospital Southampton NHS Foundation Trust
CHR3 - Sunderland Royal Hospital
CHR4 - Ashford & St Peter's Hospitals NHS Foundation Trust
CHR5 – Royal Marsden NHS Foundation Trust
CHR8 – Hampshire Hospital NHS Foundation Trust
CHR10 - Kingston Hospital NHS Foundation Trust
CHR11 – West Middlesex University Hospital
CHR12 – Kingston Hospital NHS Foundation Trust
CHR16 -King's College Hospital NHS Foundation Trust

[2] X indicates recruitment in site was paused

Table A2: Summary of Recruitment and Randomisation by Site – CHRONOS-B

Site[1]	Date site opened		COVID - 19														Total Number Recruited	Total Number Randomised
		2019	2020												2021			
		Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb		
CHR1	11/12/2019	0	2	5	2	4	2	1	4	3	2	1	0	4	1	1	32	32
CHR2	14/01/2020		0	5	0	2	4	0	0	0	0	1	0	4	4	2	22	22
CHR3	29/02/2020			0	X[2]	X[2]	X[2]	X[2]	0	0	1	1	0	0	0	0	2	2
CHR4	09/01/2020		0	0	2	0	1	2	0	0	0	0	1	0	0	0	6	6
CHR5	16/11/2020												0	0	0	0	0	0
CHR10	11/12/2020													0	1	0	1	1
CHR11	14/12/2020													0	1	0	1	1
Total		0	2	10	4	6	7	3	4	3	3	3	1	8	7	3	64	64

[1]Site Mnemonic:

CHR1 - Charing Cross Hospital
CHR2 - University Hospital Southampton NHS Foundation Trust
CHR3 - Sunderland Royal Hospital
CHR4 - Ashford and St. Peter's Hospitals (ASPH) NHS Foundation Trust
CHR5 – Royal Marsden NHS Foundation Trust
CHR10 – Kingston Hospital NHS Foundation Trust
CHR11 – West Middlesex University Hospital
[2] X indicates recruitment in site was paused

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 N=18	Radical N=18	Total N=36
Consent-Randomisation	N	18	18	36
	Min	0	0	0
	Mean (SD)	2.5 (3.13)	5.5 (6.62)	4 (5.32)
	Median (IQR)	1 (0 to 6)	4.5 (1 to 7)	1.5 (0 to 6)
	Max	9	25	25
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Randomisation - Treatment	N	16	8	24
	Min	27	31	27
	Mean (SD)	104.75 (51.49)	67 (47.73)	92.17 (52.47)
	Median (IQR)	112 (62 to 136.5)	50 (40 to 75)	85.5 (48.5 to 126.5)
	Max	209	175	209
	Missing from eCRF – n (%)	2 (11.1%)	10 (55.6%)	12 (33.3%)

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)

Visits	Statistics	Focal + finasteride N=21	Focal + bicalutamide N=21	Focal alone N=22	Total N=64
Consent-Randomisation	N	21	21	22	64
	Min	0	0	0	0
	Mean (SD)	1.57 (2.98)	2.14 (3.97)	2.45 (4.25)	2.06 (3.74)
	Median (IQR)	0 (0 to 1)	1 (0 to 2)	0 (0 to 3)	0 (0 to 2)
	Max	11	16	15	16
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Randomisation -Treatment	N	21	21	22	64
	Min	81	86	2	2
	Mean (SD)	114.81 (38.59)	114.33 (49.73)	68.55 (44.03)	98.75 (48.89)
	Median (IQR)	97 (87 to 119)	102 (92 to 117)	73.5 (20 to 93)	94.5 (84.5 to 118)
	Max	208	324	155	324
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Randomisation -Neoadjuvant Drug Treatment	N	21	21		42
	Min	0	0		0
	Mean (SD)	5.95 (11.69)	2.43 (3.83)		4.19 (8.78)
	Median (IQR)	1 (0 to 6)	0 (0 to 4)	-	0.5 (0 to 5)
	Max	49	15		49
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)		22 (34.4%)
Start of Neoadjuvant Drug Treatment - Focal Therapy	N	21	21		42
	Min	36	71		36
	Mean (SD)	108.86 (40.73)	111.9 (50.26)		110.38 (45.21)
	Median (IQR)	97 (85 to 118)	99 (92 to 117)	-	98.5 (87 to 118)
	Max	193	322		322
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)		22 (34.4%)

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[2]	Statistics	Focal N=18	Radical N=18	Total N=36
Screening Visit 1 – Visit 2	N	17	15	32
	Min	27	27	27
	Mean (SD)	106.47 (51.99)	128.87 (71.94)	116.97 (62.13)
	Median (IQR)	114 (68 to 130)	138 (41 to 181)	119 (62.5 to 164)
	Max	209	251	251
	Missing from eCRF – n (%)	1 (5.6%)	3 (16.7%)	4 (11.1%)
Visit 2 – Visit 3	N	17	13	30
	Min	57	29	29
	Mean (SD)	94.29 (25.68)	100 (55.53)	96.77 (40.59)
	Median (IQR)	90 (86 to 104)	86 (57 to 114)	89 (71 to 107)
	Max	159	244	244
	Missing from eCRF – n (%)	1 (5.6%)	5 (27.8%)	6 (16.7%)
Visit 3 – Visit 4	N	9	7	16
	Min	231	217	217
	Mean (SD)	274.56 (37.84)	254.14 (25.29)	265.63 (33.6)
	Median (IQR)	267 (244 to 308)	247 (238 to 273)	262 (241 to 288)
	Max	336	294	336
	Missing from eCRF – n (%)	9 (50.0%)	11 (61.1%)	20 (55.6%)

[1]Patients are expected to have reached Visit 3 by the end of the feasibility phase
[2]One patient in the Focal arm and two in the Radical arm have reached Visit 5

Table 2. 7: Summary statistics of time between consecutive visits (Days) from Screening Visit 1 to Visit 6[1], by treatment arm (CHRONOS-B)

Visits[2]	Statistics	Focal + finasteride N=21	Focal + bicalutamide N=21	Focal alone N=22	Total N=64
Screening Visit1 – Visit 2	N	21	21	22	64
	Min	81	61	2	2
	Mean (SD)	115.76 (39.22)	116.9 (51.5)	69.14 (43.37)	100.11 (49.68)
	Median (IQR)	97 (87 to 123)	108 (92 to 122)	73.5 (21 to 93)	94.5 (84 to 119.5)
	Max	208	324	155	324
	Missing from eCRF– n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 2 – Visit 3	N	19	20	22	61
	Min	43	66	57	43
	Mean (SD)	99.11 (38.99)	101.8 (19.1)	97.36 (22.46)	99.36 (27.41)
	Median (IQR)	92 (80 to 99)	97 (90.5 to 109)	93 (88 to 105)	95 (90 to 105)
	Max	198	143	161	198
	Missing from eCRF– n (%)	2 (9.5%)	1 (4.8%)	0 (0.0%)	3 (4.7%)
Visit 3 – Visit 4	N	18	20	22	60
	Min	84	210	191	84
	Mean (SD)	276.28 (58.88)	271.7 (24.71)	277.36 (38.18)	275.15 (41.48)
	Median (IQR)	286.5 (266 to 310)	274 (253.5 to 291)	283 (261 to 301)	279.5 (263.5 to 299)
	Max	355	314	355	355
	Missing from eCRF– n (%)	3 (14.3%)	1 (4.8%)	0 (0.0%)	4 (6.3%)
Visit 4 – Visit 5	N	18	20	20	58
	Min	63	98	49	49
	Mean (SD)	186.94 (53.37)	202.15 (43.98)	175.1 (55.12)	188.1 (51.34)
	Median (IQR)	196 (160 to 217)	199 (175.5 to 224)	183 (150.5 to 213)	189 (167 to 224)
	Max	273	304	257	304
	Missing from eCRF– n (%)	3 (14.3%)	1 (4.8%)	2 (9.1%)	6 (9.4%)
Visit 5 – Visit 6	N	12	11	12	35
	Min	50	77	0	0
	Mean (SD)	190.33 (81.34)	136.64 (39.15)	178 (89.25)	169.23 (75.48)
	Median (IQR)	185.5 (133 to 273.5)	154 (91 to 168)	188 (121 to 220)	168 (112 to 210)
	Max	301	178	315	315
	Missing from eCRF– n (%)	9 (42.9%)	10 (47.6%)	10 (45.5%)	29 (45.3%)

[1]Patients are expected to have reached Visit 3 by the end of the feasibility phase
[2]Twelve patients, four in the Focal + finasteride arm, three in the Focal + bicalutamide arm and five in Focal alone arm have reached Visit 6-Visit7

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

Treatment compliance	Focal (N=18)	Radical (N=18)	Total (N=36)
Underwent treatment[2]– n(%) 95% CI	16 (88.9%) 65.3% to 98.6%	13 (72.2%) 46.5% to 90.3%	29 (80.6%) 64% to 91.8%
Withdrawal – n (%)	0 (0.0%)	4 (22.2%)	4 (11.1%)
Screening failure– n (%)	1 (5.6%)	0 (0.0%)	1 (2.8%)

[1]Data recorded at Visit 2
[2]Reports only the number of patients who received their allocated treatment. There were two patients who did not receive their allocated treatment, one patient in each treatment arm.

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

Treatment compliance	Focal + finasteride (N=21)	Focal + bicalutamide (N=21)	Focal alone (N=22)	Total (N=64)
Underwent treatment – n (%) 95% CI	21 (100.0%) 83.9% to 1*	21 (100.0%) 83.9% to 1*	22 (100.0%) 84.6% to 1*	64 (100.0%) 94.4% to 1*
Withdrawal – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[1]Data recorded at Visit 3
(*) one-sided, 97.5% confidence interval

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

Drug compliance	Focal + Finasteride (N=21)	Focal + bicalutamide (N=21)	Focal alone	Total (N=42)
Returned empty blister packs[2] – n (%) 95% CI	7 (33.3%) 14.6% to 57%	5 (23.8%) 8.2% to 47.2%	- -	12 (28.6%) 15.7% to 44.6%
Patients who were given the drug and did not have a registered protocol deviation[3] that stated that the drug was taken for less than 8 weeks– n (%) 95% CI	21 (100.0%) 83.9% to 1*	21 (100.0%) 83.9% to 1*	- -	42 (100.0%) 84.6% to 1*

[1]Data recorded at Visit 2 and 3
[2]Returned blister packs were low due to the fact that patients avoided the clinic visits and sites were performing remote visits due to COVID
[3]There were two patients with Protocol deviation for "Dose interruptions /modifications not specified in the protocol", but the patients took the drug for more than eight weeks"
(*) one-sided, 97.5% confidence interval

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

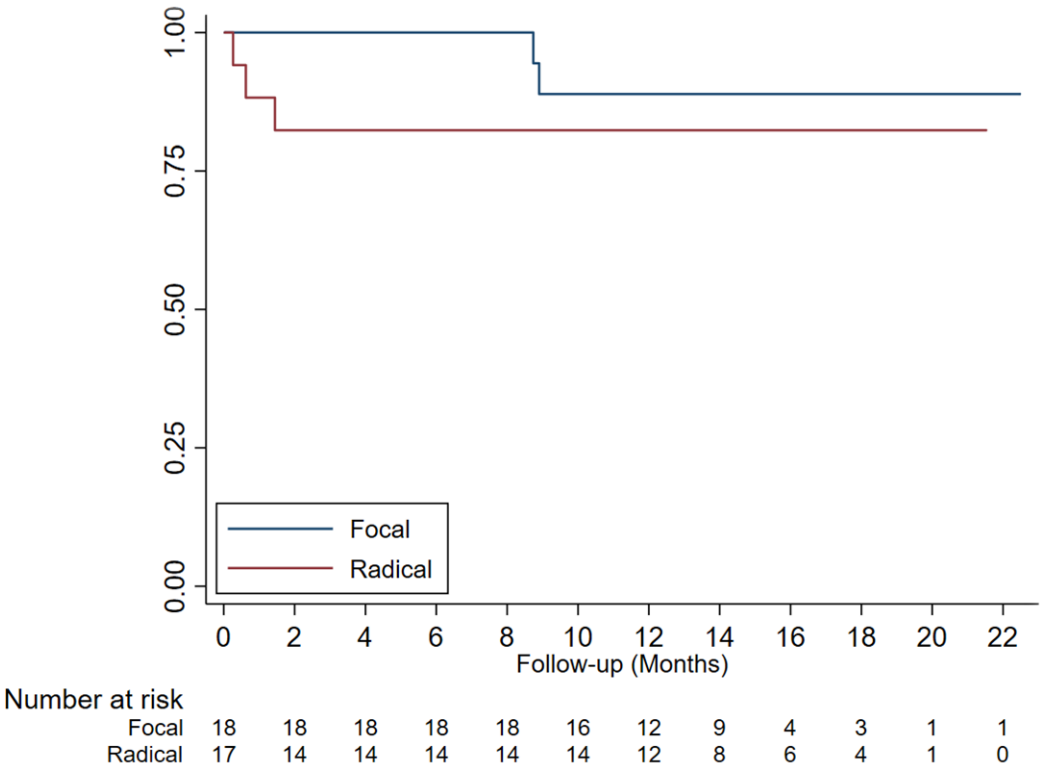
This table is not presented as only one case (CHR12-085) was recorded in Inform who failed inclusion. The reason given was "Screening Failure"

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

Reasons for withdrawal	CHRONOS A N=7	CHRONOS B N=1
Screening Failure	2* (28.6%)	0 (0.0%)
Adverse/Serious Adverse Event	0 (0.0%)	0 (0.0%)
Termination of study by sponsor	0 (0.0%)	0 (0.0%)
Investigator decision:	0 (0.0%)	0 (0.0%)
Protocol non-compliance	0 (0.0%)	0 (0.0%)
Clinical decision	0 (0.0%)	0 (0.0%)
Lost to follow up	0 (0.0%)	0 (0.0%)
Withdrawal of consent	4 (57.1%)	1 (100.0%)
Death	0 (0.0%)	0 (0.0%)
Other:	1 (14.3%)	0 (0.0%)
Total	7 (87.5%)	1 (12.5%)

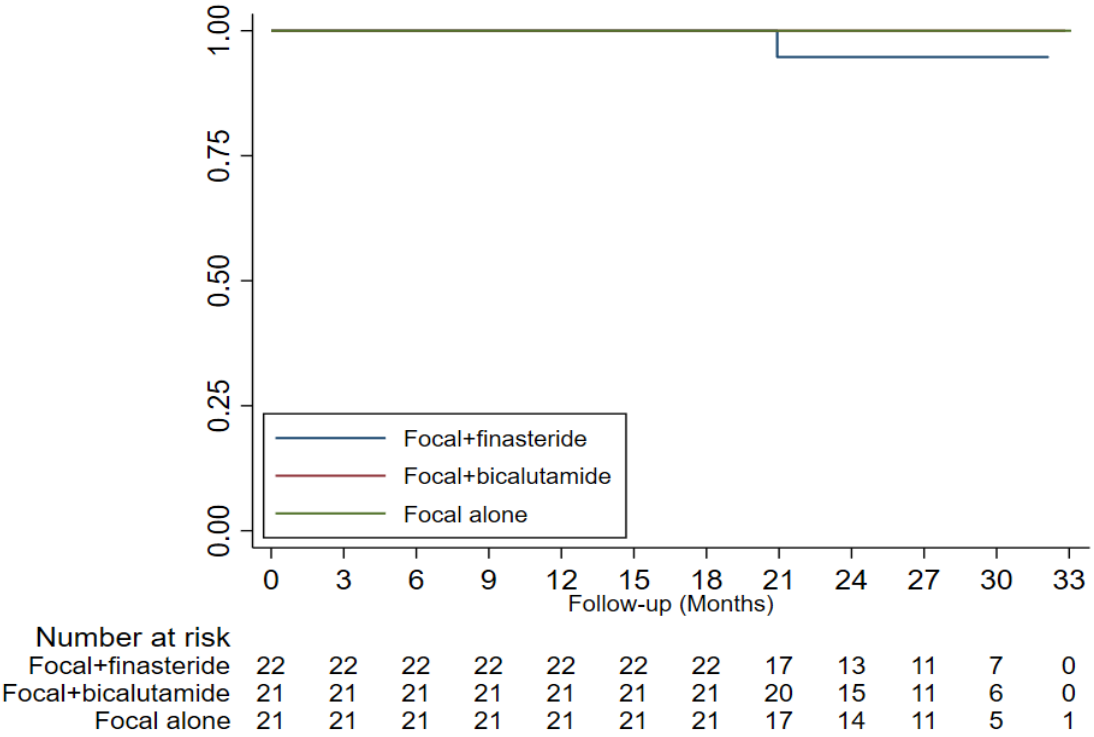
*One patient had a screening failure after consent, but before being randomised

Figure 8: Kaplan-Meier[1] plots displaying withdrawal over time (CHRONOS-A)



[1]The number at risk may be lower than the number randomised at later timepoints as not all participants have reached these timepoints while the trial is ongoing

Figure 9: Kaplan-Meier[1] plots displaying withdrawal over time and CHRONOS-B



[1]The number at risk may be lower than the number randomised at later timepoints as not all participants have reached these timepoints while the trial is ongoing

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

Variable	Statistics	Focal	Radical	Total
Age	N	1	4	5
	Mean (SD)	79.00 (.)	69.50 (7.77)	71.40 (7.96)
	Median (IQR)	79.00 (79.00-79.00)	72.50 (65.00-74.00)	73.00 (72.00-75.00)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity – n (%)	N	1	4	5
	White	0 (0.0%)	3 (75.0%)	3 (60.0%)
	Mixed	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Black	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Reported	1 (100.0%)	1 (25.0%)	2 (40.0%)
IMD Decile – n (%)	N	1	4	5
	1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	0 (0.0%)	0 (0.0%)	0 (0.0%)
	5	0 (0.0%)	1 (25.0%)	1 (20.0%)
	6	0 (0.0%)	1 (25.0%)	1 (20.0%)
	7	0 (0.0%)	0 (0.0%)	0 (0.0%)
	8	1 (100.0%)	2 (50.0%)	3 (60.0%)
	9	0 (0.0%)	0 (0.0%)	0 (0.0%)
	10	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Digital Rectal Examination – n (%)	N	1	4	5
	Yes:	1 (100.0%)	0 (0.0%)	1 (20.0%)
	Normal findings[1]	1 (100.0%)	0 (0.0%)	1 (20.0%)
	Abnormal findings[1]	0 (0.0%)	0 (0.0%)	0 (0.0%)
		0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	0 (0.0%)	4 (100.0%)	4 (80.0%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Current medications – n (%)	N	1	4	5
	Yes	1 (100.0%)	2 (50.0%)	3 (60.0%)
	No	0 (0.0%)	2 (50.0%)	2 (40.0%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5 alpha-reductase inhibitor[2] – n (%)	N	1	4	5
	Yes over (or equal to) 6 months ago	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Yes within 6 months	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	1 (100.0%)	4 (100.0%)	5 (100.0%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stratification Factors				
Tumour grade (n (%))	Gleason 3+3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Gleason 3+4	1 (100.0%)	4 (100.0%)	5 (100.0%)
	Gleason 4+3	0 (0.0%)	0 (0.0%)	0 (0.0%)
Local stage (n (%))	Clinical T2/Radiological stage <T3a	1 (100.0%)	4 (100.0%)	5 (100.0%)
	Radiological T3a	0 (0.0%)	0 (0.0%)	0 (0.0%)
Previous or current 5ARI use? (n (%))	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	1 (100.0%)	4 (100.0%)	5 (100.0%)

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

Variable	Statistics	Focal	Radical	Total
Age	N	16	14	30
	Mean (SD)	68.75 (4.16)	68.57 (7.89)	68.67 (6.07)
	Median (IQR)	69.50 (67.00-71.50)	68.00 (62.00-74.00)	68.50 (65.00-72.00)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity – n (%)	N	16	14	30
	White	12 (75.0%)	5 (35.7%)	17 (56.7%)
	Mixed	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	0 (0.0%)	1 (7.1%)	1 (3.3%)
	Black	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	0 (0.0%)	1 (7.1%)	1 (3.3%)
	Not Reported	4 (25.0%)	7 (50.0%)	11 (36.7%)
IMD Decile – n (%)	N	16	14	30
	1	0 (0.0%)	0 (0.0%)	0 (0.0%)
	2	1 (6.3%)	0 (0.0%)	1 (3.3%)
	3	1 (6.3%)	1 (7.1%)	2 (6.7%)
	4	1 (6.3%)	2 (14.3%)	3 (10.0%)
	5	2 (12.5%)	1 (7.1%)	3 (10.0%)
	6	2 (12.5%)	1 (7.1%)	3 (10.0%)
	7	4 (25.0%)	2 (14.3%)	6 (20.0%)
	8	3 (18.8%)	1 (7.1%)	4 (13.3%)
	9	0 (0.0%)	3 (21.4%)	3 (10.0%)
	10	2 (12.5%)	3 (21.4%)	5 (16.7%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Digital Rectal Examination – n (%)	N	16	14	30
	Yes:	7 (43.8%)	6 (42.9%)	13 (43.3%)
	Normal findings[1]	4 (25.0%)	3 (21.4%)	7 (23.3%)
	Abnormal findings[1]	3 (18.8%)	3 (21.4%)	6 (20.0%)
		0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	8 (50.0%)	8 (57.1%)	16 (53.3%)
	Missing from eCRF – n (%)	1 (6.3%)	0 (0.0%)	1 (3.3%)
Current medications – n (%)	N	16	14	30
	Yes	10 (62.5%)	9 (64.3%)	19 (63.3%)
	No	3 (18.8%)	3 (21.4%)	6 (20.0%)
	Missing from eCRF – n (%)	3 (18.8%)	2 (14.3%)	5 (16.7%)
5 alpha-reductase inhibitor[2] – n (%)	N	16	14	30
	Yes over (or equal to) 6 months ago	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Yes within 6 months	1 (6.3%)	0 (0.0%)	1 (3.3%)
	No	12 (75.0%)	12 (85.7%)	24 (80.0%)
	Missing from eCRF – n (%)	3 (18.8%)	2 (14.3%)	5 (16.7%)
Stratification Factors				
Tumour grade (n (%))	Gleason 3+3	1 (6.3%)	1 (7.1%)	2 (6.7%)
	Gleason 3+4	11 (68.8%)	10 (71.4%)	21 (70.0%)
	Gleason 4+3	4 (25.0%)	3 (21.4%)	7 (23.3%)
Local stage (n (%))	Clinical T2/Radiological stage <T3a	16 (100.0%)	14 (100.0%)	30 (100.0%)
	Radiological T3a	0 (0.0%)	0 (0.0%)	0 (0.0%)
Previous or current 5ARI use? (n (%))[2]	Yes	1 (6.3%)	0 (0.0%)	1 (3.3%)
	No	15 (93.8%)	14 (100.0%)	29 (96.7%)

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

This table is not presented as only one patient withdrew from CHRONOS B.

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

Variable	Statistics	Focal + finasteride	Focal + bicalutamide	Focal alone	Total
Age	N	21	21	21	63
	Mean (SD)	65.71 (6.80)	66.52 (7.53)	65.05 (6.76)	65.76 (6.95)
	Median (IQR)	67.00 (63.00-69.00)	65.00 (61.00-72.00)	65.00 (60.00-71.00)	66.00 (61.00-70.00)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity – n (%)	N	21	21	21	63
	White	15 (71.4%)	17 (81.0%)	13 (61.9%)	45 (71.4%)
	Mixed	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (1.6%)
	Asian	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (1.6%)
	Black	1 (4.8%)	1 (4.8%)	1 (4.8%)	3 (4.8%)
	Other	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (1.6%)
	Not Reported	5 (23.8%)	2 (9.5%)	5 (23.8%)	12 (19.0%)
IMD Decile – n (%)	N	21	21	21	63
	1	0 (0.0%)	2 (9.5%)	0 (0.0%)	2 (3.2%)
	2	1 (4.8%)	0 (0.0%)	2 (9.5%)	3 (4.8%)
	3	1 (4.8%)	0 (0.0%)	1 (4.8%)	2 (3.2%)
	4	6 (28.6%)	3 (14.3%)	4 (19.0%)	13 (20.6%)
	5	4 (19.0%)	3 (14.3%)	3 (14.3%)	10 (15.9%)
	6	0 (0.0%)	1 (4.8%)	3 (14.3%)	4 (6.3%)
	7	3 (14.3%)	2 (9.5%)	1 (4.8%)	6 (9.5%)
	8	3 (14.3%)	4 (19.0%)	2 (9.5%)	9 (14.3%)
	9	2 (9.5%)	2 (9.5%)	4 (19.0%)	8 (12.7%)
	10	1 (4.8%)	4 (19.0%)	1 (4.8%)	6 (9.5%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Digital Rectal Examination – n (%)	N	21	21	21	63
	Yes:	7 (33.3%)	8 (38.1%)	7 (33.3%)	22 (34.9%)
	Normal findings[1]	3 (14.3%)	6 (28.6%)	4 (19.0%)	13 (20.6%)
	Abnormal findings[1]	4 (19.0%)	2 (9.5%)	3 (14.3%)	9 (14.3%)
		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	14 (66.7%)	13 (61.9%)	14 (66.7%)	41 (65.1%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Current medications – n (%)	N	21	21	21	63
	Yes	12 (57.1%)	15 (71.4%)	13 (61.9%)	40 (63.5%)
	No	9 (42.9%)	6 (28.6%)	8 (38.1%)	23 (36.5%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5 alpha-reductase inhibitor[2] – n (%)	N	21	21	21	63
	Yes over (or equal to) 6 months ago	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (1.6%)
	Yes within 6 months	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	21 (100.0%)	20 (95.2%)	21 (100.0%)	62 (98.4%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stratification Factors					
Tumour grade (n (%))	Gleason 3+3	0 (0.0%)	2 (9.5%)	2 (9.5%)	4 (6.3%)
	Gleason 3+4	17 (81.0%)	16 (76.2%)	15 (71.4%)	48 (76.2%)
	Gleason 4+3	4 (19.0%)	3 (14.3%)	4 (19.0%)	11 (17.5%)
Local stage (n (%))	Clinical T2/Radiological stage <T3a	18 (85.7%)	19 (90.5%)	20 (95.2%)	57 (90.5%)
	Radiological T3a	3 (14.3%)	2 (9.5%)	1 (4.8%)	6 (9.5%)

[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 2. 17 - CHRONOS A: Listing of all Adverse Events

Treatment group	Subject ID	Site	AE Number	AE Term	Onset Date	End Date	Ongoing	Severity[2]	Relationship to Study IMP	Action Taken Concerning Study IMP	Outcome	Serious ?
Focal	CHR2-096	CHR2	1	stroke	15/11/2021	16/11/2021	No	Mild	Not related	None	Resolved	No
Focal	CHR3-080	CHR3	1	Abdominal pain	01/12/2021	02/12/2021	No	Mild	Unlikely	None	Resolved	No
Focal	CHR3-080	CHR3	2	COVID	30/03/2022	06/04/2022	No	Mild	Unlikely	None	Resolved	No
Focal	CHR3-080	CHR3	3	Chest infection	17/07/2022	29/07/2022	No	Mild	Unlikely	None	Resolved	No
Focal	CHR3-083	CHR3	1	Hypercholesterolaemia	18/10/2021		Yes	Mild	Unlikely	None	Not assessable	No
Focal	CHR3-091	CHR3	1	Infection following tooth extraction	29/03/2022	05/04/2022	No	Mild	Unlikely	None	Resolved	No
Focal	CHR11-068	CHR11	1	History of haemospermia, dysuria, and tiredness for 5 weeks. Flexible cystoscopy was performed on 8/11/22. Diagnosed with UTI. Co-amoxiclav 625 mg tds for 10 days prescribed.	08/11/2022	18/11/2022	No	Moderate	Definitely	None	Resolved	No
Focal	CHR2-099	CHR2	1	Iatrogenic Scrotal Oedema	30/12/2021	31/12/2021	No	Moderate	Not related	None	Resolved	Yes
Radical	CHR2-081	CHR2	1	Acute Urinary retention	24/12/2021	25/12/2021	No	Mild	Not related	None	Resolved with sequelae	Yes
Radical	CHR2-081	CHR2	2	Paraphimosis	16/01/2022	17/01/2022	No	Moderate	Not related	None	Resolved	Yes
Radical	CHR8-097	CHR8	1	Patient presented to hospital 01/08- 04/08 with worsening haematuria following a cystoscopy which identified a bladder malignancy. Pt also had TURBT 03/08.	01/08/2022	04/08/2022	No	Severe	Not related	None	Resolved	No

[1]Site Mnemonic:
CHR2 - University Hospital Southampton NHS Foundation Trust
CHR3 - Sunderland Royal Hospital
CHR8 – Hampshire Hospital NHS Foundation Trust

Table 2. 18 - CHRONOS A: Summary of Adverse Events[1] by Severity Grade (v4.0 CTCAE), by Treatment Arm

	Subjects with at least one AEs[2]						
Severity Grade of AE	**1=Mild**	**2=Moderate**	**3=Severe**	**4**	**5**	**Missing**	**Total**
Treatment							
Focal	4 (100.0%)	2 (66.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (75.0%)
Radical	0 (0.0%)	1 (33.3%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)
All subjects	**4 (50.0%)**	**3 (37.5%)**	**1 (12.5%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**8 (100.0%)**

	All AEs (patients could have had more than one AE)						
Severity Grade of AE	**1=Mild**	**2=Moderate**	**3=Severe**	**4**	**5**	**Missing**	**Total**
Treatment							
Focal	6 (85.7%)	2 (66.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (72.7%)
Radical	1 (14.3%)	1 (33.3%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (27.3%)
Total	**7 (63.6%)**	**3 (27.3%)**	**1 (9.1%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**11 (100.0%)**

[1]Expected adverse events which will not be reported are listed in Appendix 1
[2]Where subjects have more than one AE, the highest severity grade has been used

Table 2. 19 - CHRONOS A: Number of Adverse Events[1] by Relationship to study treatment, by Treatment Arm

	Subjects with at least one AEs[2]							
Relationship to study	**Definitely**	**Probably**	**Possibly**	**Unlikely**	**Not related**	**Not assessable**	**Missing**	**Total**
Treatment								
Focal	1 (100.0%)	0 (0.0%)	0 (0.0%)	3 (100.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)	6 (75.0%)
Radical	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)
All subjects	**1 (12.5%)**	**0 (0.0%)**	**0 (0.0%)**	**3 (37.5%)**	**4 (50.0%)**	**0 (0.0%)**	**0 (0.0%)**	**8 (100.0%)**

	All AEs (patients could have had more than one AE)							
Relationship to study	**Definitely**	**Probably**	**Possibly**	**Unlikely**	**Not related**	**Not assessable**	**Missing**	**Total**
Treatment								
Focal	1 (100.0%)	0 (0.0%)	0 (0.0%)	5 (100.0%)	2 (40.0%)	0 (0.0%)	0 (0.0%)	8 (72.7%)
Radical	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (60.0%)	0 (0.0%)	0 (0.0%)	3 (27.3%)
Total	**1 (9.1%)**	**0 (0.0%)**	**0 (0.0%)**	**5 (45.5%)**	**5 (45.5%)**	**0 (0.0%)**	**0 (0.0%)**	**11 (100.0%)**

[1]Expected adverse events which will not be reported are listed in Appendix 1
[2]Where subjects have more than one AE, the highest relationship has been used

Table 2. 20 – CHRONOS A: Listing of all Serious Adverse Events by Category

Treatment group	Subject ID	Site[1]	SAE No.	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
Focal	CHR2-099	CHR2	1	Iatrogenic scrotal oedema (Primary)	Admitted with scrotal oedema and cellulitis one week post cryotherapy for prostate cancer. On examination the was significant scrotal oedema with mild penile shaft involvement. Observations and blood tests unremarkable. Oedema improved with scotal support. He was treated with Flucaxcillian to cover for cellulitis	04/01/2022	Required inpatient hospitalisation or prolongation of existing hospitalisation	30/12/2021	Moderate	Resolved	31/12/2021	Definitely	Unexpected	None
Radical	CHR2-081	CHR2	1	Acute Urinary retention	Patient was admitted with lower abdominal pain and difficulty passing urine. Bloods (including renal function) and examination were unremarkable. Bladder scan showed 1000ml volume and so he was catheterised overnight, and well enough to be discharged home 25/12/21 with advice to continue Tamsulosin. A referral has been made to the district nurse team for ongoing catheter care.	04/01/2022	Required inpatient hospitalisation or prolongation of existing hospitalisation	24/12/2021	Moderate	Resolved with sequelae	25/12/2021	Probably	Expected	None
Radical	CHR2-081	CHR2	2	Paraphimosis	Patient CHR2-081 was admitted with paraphimosis post catheter change earlier in the day. He was reviewed by urology, and they eventually manage to reduce the paraphimosis under local anaesthetic. He was observed closely following the procedure and it has remained settled. He is to have 5 days of cefalexin as per urology and has been booked into follow up with them.	25/01/2022	Required inpatient hospitalisation or prolongation of existing hospitalisation	16/01/2022	Moderate	Resolved	17/01/2022	Definitely	Expected	None

[1]Site Mnemonic:

CHR2 - University Hospital Southampton NHS Foundation Trust

Table 2. 21 - CHRONOS A: Summary of Serious Adverse Events by Category, by Treatment Arm

	Subjects with at least one SAEs[1]						
Category of SAEs	**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**	**Total**
Treatment							
Focal	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
Radical	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
All subjects	**0 (0.0%)**	**0 (0.0%)**	**2 (100.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (100.0%)**

	All SAEs (patients could have had more than one SAE)						
Category of SAEs	**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**	**Total**
Treatment							
Focal	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
Radical	0 (0.0%)	0 (0.0%)	2 (66.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (66.7%)
Total	**0 (0.0%)**	**0 (0.0%)**	**3 (100.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**3 (100.0%)**

[1]Where subjects have more than one SAE, only the highest category has been reported

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

	Subjects with at least one SAEs[1]						
Causal Relationship	**Definitely**	**Probably**	**Possibly**	**Unlikely**	**Not related**	**Not assessable**	**Total**
Treatment							
Focal	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
Radical	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
All subjects	**2 (100.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**2 (100.0%)**

	All SAEs (patients could have had more than one SAE)						
Causal Relationship	**Definitely**	**Probably**	**Possibly**	**Unlikely**	**Not related**	**Not assessable**	**Total**
Treatment							
Focal	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
Radical	1 (50.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (66.7%)
Total	**2 (66.7%)**	**1 (33.3%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**3 (100.0%)**

[1]Where subjects have more than one SAE, only the highest relationship has been reported

Table 2. 23 - CHRONOS B: Listing of all Adverse Events

Treatment group	Subject ID	Site	AE No.	AE Term	Onset Date	End Date	Ongoing	Severity	Relationship to Study IMP	Action Taken Concerning Study IMP	Outcome	Serious?
Focal + finasteride	CHR1-021	CHR1	2	Erectile Dysfunction	16/07/2020		Yes	Mild	Not related	None	Persisting	No
Focal + finasteride	CHR1-021	CHR1	3	Dry Orgasm	16/07/2020		Yes	Mild	Not related	None	Persisting	No
Focal + finasteride	CHR2-006	CHR2	1	Head injury	09/04/2022	09/04/2022	No	Mild	Not related	None	Resolved	No
Focal + finasteride	CHR2-045	CHR2	1	pancytopenia	24/12/2020		Yes	Mild	Not related	None	Not assessable	No
Focal + finasteride	CHR1-001	CHR1	2	Haematuria	12/04/2020	12/04/2020	No	Mild	Probable	None	Resolved	No
Focal + finasteride	CHR1-021	CHR1	1	Painless swelling and mild bruising of scrotal and penile skin	21/07/2020	01/07/2020	No	Mild	Unlikely	None	Resolved	No
Focal + finasteride	CHR1-040	CHR1	1	Low urinary flow rate	03/12/2020		Yes	Mild	Unlikely	None	Persisting	No
Focal + finasteride	CHR1-048	CHR1	1	Haemtospermia	09/03/2021	26/04/2021	No	Mild	Unlikely	None	Resolved	No
Focal + finasteride	CHR1-048	CHR1	2	Haematuria	09/03/2021	26/04/2021	No	Mild	Unlikely	None	Resolved	No
Focal + finasteride	CHR4-031	CHR4	1	Fatigue	20/08/2020	23/06/2021	No	Moderate	Possible	Permanently discontinued	Resolved	No
Focal + finasteride	CHR1-001	CHR1	1	UTI, epididymo-orchitis	22/04/2020	22/05/2020	No	Moderate	Probable	None	Resolved	No
Focal + finasteride	CHR1-001	CHR1	3	Nocturia	05/08/2021		Yes	Moderate	Unlikely	None	Persisting	No
Focal + finasteride	CHR1-014	CHR1	1	Urinary Retention	20/08/2020	23/08/2020	No	Moderate	Unlikely	None	Resolved	No
Focal + finasteride	CHR1-014	CHR1	2	Urinary tract infection	18/08/2020	30/08/2020	No	Moderate	Unlikely	None	Resolved	No
Focal + finasteride	CHR1-027	CHR1	1	Erectile Dysfunction	01/01/2021		Yes	Moderate	Unlikely	None	Persisting	No
Focal + finasteride	CHR1-004	CHR1	1	Lower Urinary Tract Symptoms	28/05/2020		Yes	Missing	Missing	None	Missing	No
Focal + finasteride	CHR1-036	CHR1	1	Erectile Dysfunction	05/01/2022		Yes	Missing	Missing	None	Persisting	No
Focal + finasteride	CHR1-039	CHR1	1	Post HIFU Prostate Inflammation	22/03/2021	16/07/2021	No	Missing	Missing	None	Resolved	No
Focal + finasteride	CHR1-039	CHR1	2	Blood from urethral meatus when straining	10/11/2022		Yes	Missing	Missing	None	Missing	
Focal + bicalutamide	CHR2-024	CHR2	1	Urinary retention	10/12/2021	10/12/2021	No	Mild	Definite	None	Resolved	No

Focal + bicalutamide	CHR1-044	CHR1	2	Elective (planned) parathyroidectomy	01/02/2021	01/02/2021	No	Mild	Not related	None	Resolved	No
Focal + bicalutamide	CHR11-064	CHR11	1	Admitted to ER with 18-20 hrs of urinary retention. Passed urine in ER. Discharged	09/09/2022	09/09/2022	No	Mild	Not related	None	Resolved	No
Focal + bicalutamide	CHR3-042	CHR3	2	Urinary tract infection	17/02/2021	24/02/2021	No	Mild	Not related	None	Resolved	No
Focal + bicalutamide	CHR1-018	CHR1	1	Painful nipples	22/06/2020	02/12/2020	No	Mild	Probable	None	Resolved	No
Focal + bicalutamide	CHR1-034	CHR1	2	Allergic reaction to Penicillin	16/10/2020	01/10/2020	No	Mild	Unlikely	None	Resolved	No
Focal + bicalutamide	CHR1-044	CHR1	1	Ejaculatory dysfunction	21/01/2021		Yes	Mild	Unlikely	None	Persisting	No
Focal + bicalutamide	CHR1-050	CHR1	2	Depression	25/03/2021		Yes	Mild	Unlikely	None	Persisting	No
Focal + bicalutamide	CHR1-057	CHR1	2	Penile tip pain	01/04/2021		Yes	Mild	Unlikely	None	Persisting	No
Focal + bicalutamide	CHR3-042	CHR3	6	E. coli urinary tract infection	20/12/2021	07/01/2022	No	Mild	Unlikely	None	Resolved	No
Focal + bicalutamide	CHR3-042	CHR3	8	Urgency of micturition	20/09/2021		Yes	Mild	Unlikely	None	Persisting	No
Focal + bicalutamide	CHR3-042	CHR3	9	Dry ongoing cough, Chest xray clear	24/11/2021	20/12/2021	No	Mild	Unlikely	None	Resolved	No
Focal + bicalutamide	CHR3-042	CHR3	11	Urinary Tract Infection	14/02/2022	28/02/2022	No	Mild	Unlikely	None	Resolved	No
Focal + bicalutamide	CHR3-042	CHR3	12	Urinary tract infection	03/03/2022	18/03/2022	No	Mild	Unlikely	None	Resolved	No
Focal + bicalutamide	CHR3-042	CHR3	13	Recurrent urinary tract infections	22/03/2022		Yes	Mild	Unlikely	None	Not assessable	No
Focal + bicalutamide	CHR3-042	CHR3	16	Urinary tract infection	28/07/2022	26/08/2022	No	Mild	Unlikely	None	Resolved	No
Focal + bicalutamide	CHR2-005	CHR2	1	Visible haematuria	14/09/2022	17/09/2022	No	Moderate	Not related	None	Resolved	Yes
Focal + bicalutamide	CHR2-005	CHR2	2	Visible Haematuria	03/11/2022	05/11/2022	No	Moderate	Not related	None	Resolved	No
Focal + bicalutamide	CHR3-042	CHR3	3	Abdominal pain	19/04/2021	28/05/2021	No	Moderate	Not related	Other	Resolved	Yes
Focal + bicalutamide	CHR3-042	CHR3	14	Infection due to common bile duct stones	13/04/2022	20/04/2022	No	Moderate	Not related	None	Resolved	Yes
Focal + bicalutamide	CHR3-042	CHR3	19	Removal of stones from common bile duct	07/11/2022	07/11/2022	No	Moderate	Not related	None	Resolved	Yes
Focal + bicalutamide	CHR1-018	CHR1	2	Erectile Dysfunction	13/07/2020		Yes	Moderate	Possible	None	Persisting	No

Focal + bicalutamide	CHR1-038	CHR1	1	Erectile dysfunction	07/12/2020		Yes	Moderate	Possible	None	Persisting	No
Focal + bicalutamide	CHR1-002	CHR1	1	Complications of urinary catheter	12/06/2020	26/06/2020	No	Moderate	Probable	None	Resolved	No
Focal + bicalutamide	CHR1-037	CHR1	1	Erectile dysfunction	06/11/2020		Yes	Moderate	Probable	None	Persisting	No
Focal + bicalutamide	CHR1-034	CHR1	1	Urinary tract infection	16/10/2020	01/10/2020	No	Moderate	Unlikely	None	Resolved	No
Focal + bicalutamide	CHR1-050	CHR1	1	Short term memory loss	25/03/2021		Yes	Moderate	Unlikely	None	Persisting	No
Focal + bicalutamide	CHR1-050	CHR1	3	Post traumatic stress disorder	25/03/2021		Yes	Moderate	Unlikely	None	Persisting	No
Focal + bicalutamide	CHR1-057	CHR1	1	Complication of urinary catheter	23/04/2021	23/04/2021	No	Moderate	Unlikely	None	Resolved	No
Focal + bicalutamide	CHR3-042	CHR3	1	Torsades de Pointes	18/12/2020	30/12/2020	No	Moderate	Unlikely	None	Resolved	Yes
Focal + bicalutamide	CHR3-042	CHR3	7	Suspected common bile duct stone/pancreatitis,serum amylase raised	07/01/2022	11/01/2022	No	Moderate	Unlikely	None	Resolved	No
Focal + bicalutamide	CHR3-042	CHR3	10	Urinary tract infection	27/01/2022	10/02/2022	No	Moderate	Unlikely	None	Resolved	No
Focal + bicalutamide	CHR3-042	CHR3	15	Failed removal of common bile duct stones	15/08/2022	20/08/2022	No	Moderate	Unlikely	None	Resolved	Yes
Focal + bicalutamide	CHR3-042	CHR3	18	Rectal fissure	05/09/2022		Yes	Moderate	Unlikely	None	Not assessable	
Focal + bicalutamide	CHR3-043	CHR3	1	Campylobacter	13/06/2022	11/07/2022	No	Moderate	Unlikely	None	Resolved	No
Focal + bicalutamide	CHR4-013	CHR4	1	Urine retention after trial without catheter following High Intensity Focussed Ultrasound - required re-catheterisation in Accident and Emergency	16/07/2020	13/10/2020	No	Moderate	Unlikely	None	Resolved	No
Focal + bicalutamide	CHR4-032	CHR4	1	Aortic stenosis	26/10/2020	27/01/2021	No	Severe	Not related	Temporarily discontinued	Resolved	Yes
Focal + bicalutamide	CHR1-002	CHR1	2	Prostatitis	13/07/2022	03/08/2022	No	Missing	Missing	None	Resolved	No
Focal + bicalutamide	CHR1-008	CHR1	1	Erectile Dysfunction	04/11/2021		Yes	Missing	Missing	None	Persisting	No
Focal + bicalutamide	CHR1-017	CHR1	1	Knee Replacement	01/08/2022	01/08/2022	No	Missing	Missing	None	Resolved	No

Focal + bicalutamide	CHR1-050	CHR1	4	Erectile Dysfunction	20/09/2021		Yes	Missing	Missing	None	Missing	No
Focal + bicalutamide	CHR1-051	CHR1	1	Erectile Dysfunction	30/03/2022		Yes	Missing	Missing	None	Persisting	No
Focal alone	CHR1-019	CHR1	6	Worsening night sweats	11/06/2020		Yes	Mild	Probable	None	Resolved	No
Focal alone	CHR1-019	CHR1	4	Swollen testicles	11/06/2020	01/10/2020	No	Mild	Unlikely	None	Resolved	No
Focal alone	CHR1-019	CHR1	5	Sweaty testicles	11/06/2020		Yes	Mild	Unlikely	None	Resolved	No
Focal alone	CHR1-020	CHR1	3	Lower urinary tract symptoms	13/07/2020	01/08/2021	No	Mild	Unlikely	None	Resolved	No
Focal alone	CHR1-041	CHR1	1	Penile numbness	26/01/2021		Yes	Mild	Unlikely	None	Persisting	No
Focal alone	CHR1-020	CHR1	2	Erectile Dysfunction	13/07/2020		Yes	Moderate	Not related	None	Persisting	No
Focal alone	CHR1-033	CHR1	1	Erectile Dysfunction	24/09/2020		Yes	Moderate	Not related	None	Persisting	No
Focal alone	CHR2-011	CHR2	2	Lower urinary tract infection,	05/05/2022	05/05/2022	No	Moderate	Not related	None	Resolved	No
Focal alone	CHR4-015	CHR4	1	Urine leaking around catheter - ?catheter blocked, requires flushing.	10/07/2020	10/07/2020	No	Moderate	Not related	None	Resolved	No
Focal alone	CHR2-011	CHR2	1	Bacterial Cellulitis and Related Conditions	19/04/2022	23/04/2022	No	Moderate	Possible	None	Resolved	Yes
Focal alone	CHR1-003	CHR1	2	Severe LUTS	15/05/2020	02/06/2020	No	Moderate	Probable	None	Resolved	No
Focal alone	CHR1-019	CHR1	1	Constipation	11/06/2020	31/08/2020	No	Moderate	Unlikely	None	Resolved	No
Focal alone	CHR1-019	CHR1	2	Genitourinary infection	15/06/2020	01/07/2020	No	Moderate	Unlikely	None	Resolved	No
Focal alone	CHR1-019	CHR1	3	Lower Urinary tract symptoms	11/06/2020		Yes	Moderate	Unlikely	None	Persisting	No
Focal alone	CHR1-020	CHR1	1	Epididymo-orchitis	01/09/2020	01/10/2020	No	Moderate	Unlikely	None	Resolved	No
Focal alone	CHR1-035	CHR1	1	Reaction to Ciprofloxacin (Nausea and Vomiting)	01/11/2020	01/11/2020	No	Moderate	Unlikely	None	Resolved	No
Focal alone	CHR1-062	CHR1	1	Urinary retention	06/04/2021	20/04/2021	No	Moderate	Unlikely	None	Resolved	No
Focal alone	CHR1-003	CHR1	1	patient required TURP after urosepsis and retention	02/06/2020	25/06/2020	No	Severe	Not related	None	Resolved	Yes

Focal alone	CHR4-015	CHR4	2	Pleuritic Chest Pain - Bilateral pulmonary emboli on CT imaging	03/10/2021	10/10/2021	No	Severe	Unlikely	None	Resolved with sequelae	Yes
Focal alone	CHR1-016	CHR1	1	Erectile Dysfunction	20/10/2021		Yes	Missing	Missing	None	Persisting	No
Focal alone	CHR1-019	CHR1	7	Erectile Dysfunction	28/10/2020		Yes	Missing	Missing	None	Persisting	No
Focal alone	CHR1-035	CHR1	2	Erectile Dysfunction	01/01/2022		Yes	Missing	Missing	None	Missing	No
Focal alone	CHR1-035	CHR1	3	Lower Urinary Tract Symptoms	01/11/2020		Yes	Missing	Missing	None	Missing	No
Focal alone	CHR1-062	CHR1	2	Erectile Dysfunction	21/07/2021		Yes	Missing	Missing	None	Missing	No

[1]Site Mnemonic:

CHR1 - Charing Cross Hospital
CHR2 - University Hospital Southampton NHS Foundation Trust
CHR3 - Sunderland Royal Hospital
CHR4 - Ashford & St Peter's Hospitals NHS Foundation Trust

Table 2. 24 - CHRONOS B: Summary of Adverse Events[1] by Severity Grade (v4.0 CTCAE), by Treatment Arm

	Subjects with at least one AEs[2]						
Severity Grade of AE	**1=Mild**	**2=Moderate**	**3=Severe**	**4**	**5**	**Missing**	**Total**
Treatment							
Focal alone	1 (11.1%)	3 (18.8%)	2 (66.7%)	0 (0.0%)	0 (0.0%)	4 (33.3%)	10 (25.0%)
Focal + finasteride	5 (55.6%)	4 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (25.0%)	12 (30.0%)
Focal + bicalutamide	3 (33.3%)	9 (56.3%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	5 (41.7%)	18 (45.0%)
All subjects	**9 (22.5%)**	**16 (40.0%)**	**3 (7.5%)**	**0 (0.0%)**	**0 (0.0%)**	**12 (30.0%)**	**40 (100.0%)**

	All AEs (patients could have had more than one AE)						
Severity Grade of AE	**1=Mild**	**2=Moderate**	**3=Severe**	**4**	**5**	**Missing**	**Total**
Treatment							
Focal alone	5 (16.7%)	12 (31.6%)	2 (66.7%)	0 (0.0%)	0 (0.0%)	5 (35.7%)	24 (28.2%)
Focal + finasteride	9 (30.0%)	6 (15.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (28.6%)	19 (22.4%)
Focal + bicalutamide	16 (53.3%)	20 (52.6%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	5 (35.7%)	42 (49.4%)
Total	**30 (35.3%)**	**38 (44.7%)**	**3 (3.5%)**	**0 (0.0%)**	**0 (0.0%)**	**14 (16.5%)**	**85 (100.0%)**

[1]Expected adverse events which will not be reported are listed in Appendix 1
[2]Where subjects have more than one AE, the highest severity grade has been used

Table 2. 25 - CHRONOS B: Number of Adverse Events[1] by Relationship to study treatment, by Treatment Arm

	Subjects with at least one AEs[2]							
Relationship to study	**Definitely**	**Probably**	**Possibly**	**Unlikely**	**Not related**	**Not assessable**	**Missing**	**Total**
Treatment								
Focal alone	0 (0.0%)	2 (33.3%)	1 (33.3%)	5 (29.4%)	1 (16.7%)	0 (0.0%)	1 (14.3%)	10 (25.0%)
Focal + finasteride	0 (0.0%)	1 (16.7%)	1 (33.3%)	5 (29.4%)	2 (33.3%)	0 (0.0%)	3 (42.9%)	12 (30.0%)
Focal + bicalutamide	1 (100.0%)	3 (50.0%)	1 (33.3%)	7 (41.2%)	3 (50.0%)	0 (0.0%)	3 (42.9%)	18 (45.0%)
All subjects	**1 (2.5%)**	**6 (15.0%)**	**3 (7.5%)**	**17 (42.5%)**	**6 (15.0%)**	**0 (0.0%)**	**7 (17.5%)**	**40 (100.0%)**

	All AEs (patients could have had more than one AE)							
Relationship to study	**Definitely**	**Probably**	**Possibly**	**Unlikely**	**Not related**	**Not assessable**	**Missing**	**Total**
Treatment								
Focal alone	0 (0.0%)	2 (28.6%)	1 (25.0%)	11 (26.8%)	5 (27.8%)	0 (0.0%)	5 (35.7%)	24 (28.2%)
Focal + finasteride	0 (0.0%)	2 (28.6%)	1 (25.0%)	8 (19.5%)	4 (22.2%)	0 (0.0%)	4 (28.6%)	19 (22.4%)
Focal + bicalutamide	1 (100.0%)	3 (42.9%)	2 (50.0%)	22 (53.7%)	9 (50.0%)	0 (0.0%)	5 (35.7%)	42 (49.4%)
Total	**1 (1.2%)**	**7 (8.2%)**	**4 (4.7%)**	**41 (48.2%)**	**18 (21.2%)**	**0 (0.0%)**	**14 (16.5%)**	**85 (100.0%)**

[1]Expected adverse events which will not be reported are listed in Appendix 1
[2]Where subjects have more than one AE, the highest relationship has been used

Table 2. 26 – CHRONOS B: Listing of all Serious Adverse Events by Category

Treatment group	Subject ID	Site	SAE No.	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
Focal alone	CHR1-003	CHR1	1	Admission for urosepsis	Patient went into retention secondary to urinary tract infection. Required 3 day admission for IV antibiotics	10/06/2020	Required inpatient hospitalisation or prolongation of existing hospitalisation	03/06/2020	Moderate	Resolved with sequelae	19/06/2020	Definite	Expected	None
Focal alone	CHR2-011	CHR2	1	Bacterial Cellulitis and Related Conditi	Admitted with erythema of penis, scrotum, perineum and suprapubic area with penile discharge. Bloods were unremarkable, observations stable, afebrile. Treated as cellulitis with flucloxacillin then escalated to Tazocin and Clindamycin on microbiology advice. Catheterised. Penile swab returned staph aureus. CT performed which showed no radiologically concerning features such as subcutaneous gas or organised collections. MRI prostate performed to rule out fistula. No evidence of fistula/prostatic abscess. Erythema improved and antibiotics reverted to flucloxacillin. Medically fit for discharge with the following plan in place	25/04/2022	Required inpatient hospitalisation or prolongation of existing hospitalisation	19/04/2022	Moderate	Resolved	23/04/2022	Unlikely	Unexpected	None
Focal alone	CHR4-015	CHR4	1	Pleuritic chest pain	5 day history of indigestion, central chest pressure and left sided neck ache. Computed tomography Pulmonary angiogram done in hospital and multiple Pulmonrary emboli found. Started on clexane 105mg subcutaneously then apixaban 5mg oral twice daily. Awaiting Magnetic resonance imaging of prostate.	07/10/2021	Required inpatient hospitalisation or prolongation of existing hospitalisation	01/10/2021	Severe	Resolved	11/10/2021	Not related	Unexpected	None

Focal + bicalutamide	CHR2-005	CHR2	1	Visible haematuria	patient presented with haematuria and passing clots on 13/09. Urinanalysis showed +ve for leucocytes and nitrites. Bloods NAD Hb 150. Haemodynamically stable. Patient was given stat gent. Catheterised with a 3-way for irrigation. Aspirin held.14/09: Patient normotensive and apyrexial. Haematuria ongoing - continue irrigation. 15/09: Urine clear. Twoc'd successfully. 16/09: patient had a CT urogram performed to which he had a reaction (hives and neck rash) to the contrast. He was given some anti-histamines and is now clinically well. He has received some safety netting advice regarding the matter.Patient is now medically fit for discharge. Aspirin to be restarted 24hrs post discharge.	21/09/2022	Required inpatient hospitalisation or prolongation of existing hospitalisation	14/09/2022	Moderate	Resolved	17/09/2022	Not related	Unexpected	None
Focal + bicalutamide	CHR3-042	CHR3	1	Torsades de Pointes	Had a collapse and dizzy spells at home. Admitted 18/12/20 with holster monitor showing torsades de pointes. Low magnesium corrected. Angiogram showed normal coronaries and long qTC ? due to bicalutamide. Single chamber ICD inserted on 29/12/20. Also had COVID.	09/02/2021	Required inpatient hospitalisation or prolongation of existing hospitalisation	18/12/2020	Moderate	Resolved	30/12/2020	Not related	Unexpected	None
Focal + bicalutamide	CHR3-042	CHR3	2	Abdominal pain	2x discrete episodes of 10/10 abdominal pain on 19/4/21 for 2 hours and 20/4/21 from 0500 until 0830 - woke him up. Quite abrupt onset. Entire abdomen, symmetrical 10/10 pain. Writhing in pain, unable to get comfortable at time. Sweaty, clammy, pale	22/04/2021	Required inpatient hospitalisation or prolongation of existing hospitalisation	19/04/2021	Moderate	Resolved	28/05/2021	Not related	Unexpected	None

					looking according to wife at time. Nauseated but didn't vomit. Abdomen felt rigid and distended. Bowels opened yesterday dinner time- normal for him. Today - only small amounts of mucus, Is passing flatus ok. Attended A & E 20/4/21 Bloods taken and CT abdomen and pelvis performed, and ECG. Patient was sent home and asked to come back the next day for investigation results. Newly deranged LFTs, Mildly WCC and neutrophils and CRP. Was found to have E. coli in urine microbiology and blood cultures. 21/4/21 Bloods repeated - CRP increased to 135, Diagnosed as intra-abdominal infection. Had Ultrasound scan - no evidence of CBD stones. Admitted for intravenous antibiotics. Pain ? biliary in nature. For transfer to the Freeman Hospital for ERCP. 28/4/21 Transferred to the Freeman Hospital in Newcastle. 28/5/21 Had ultrasound and ERPC which was NAD. Situation resolved										
Focal + bicalutamide	CHR3-042	CHR3	3	Infection due to common bile duct stones	Patient experienced upper abdominal pain, vomiting and jaundice. Attended A & E. Bilirubin and ALT levels raised. Given IV antibiotics and analgesia and discharged home on oral antibiotics on 15/4/22	21/04/2022	Required inpatient hospitalisation or prolongation of existing hospitalisation	13/04/2022	Moderate	Resolved	20/04/2022	Not related	Unexpected	None
Focal + bicalutamide	CHR3-042	CHR3	4	Hospitalised	Hospitalised for removal of CBD stones which failed but CBD was stented	06/12/2022	Required inpatient hospitalisation or	15/08/2022	Moderate	Resolved	20/08/2022	Not related	Unexpected	None

							prolongation of existing hospitalisation							
Focal + bicalutamide	CHR3-042	CHR3	5	Common bile duct stones	Admitted to hospital for removal of stones from common bile duct	15/12/2022	Required inpatient hospitalisation or prolongation of existing hospitalisation	07/11/2022	Moderate	Resolved	07/11/2022	Not related	Unexpected	None
Focal + bicalutamide	CHR4-032	CHR4	1	Aortic stenosis	Found to have heart murmur on initial planned day of cryotherapy. Investigations by Cardiology found severe aortic stenosis requiring intervention	17/08/2021	Other medically important event	23/09/2020	Severe	Resolved	27/01/2021	Not related	Unexpected	Treatment permanently stopped

[1]Site Mnemonic:

CHR1 - Charing Cross Hospital
CHR2 - University Hospital Southampton NHS Foundation Trust
CHR3 - Sunderland Royal Hospital
CHR4 - Ashford & St Peter's Hospitals NHS Foundation Trust

Table 2. 27 - CHRONOS B: Summary of Serious Adverse Events by Category, by Treatment Arm

	Subjects with at least one SAEs[1]						
Category of SAEs	**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**	**Total**
Treatment							
Focal alone	0 (0.0%)	0 (0.0%)	3 (60.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (50.0%)
Focal + finasteride	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Focal + bicalutamide	0 (0.0%)	0 (0.0%)	2 (40.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	3 (50.0%)
All subjects	**0 (0.0%)**	**0 (0.0%)**	**5 (83.3%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (16.7%)**	**6 (100.0%)**

	All SAEs (patients could have had more than one SAE)						
Category of SAEs	**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**	**Total**
Treatment							
Focal alone	0 (0.0%)	0 (0.0%)	3 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (30.0%)
Focal + finasteride	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Focal + bicalutamide	0 (0.0%)	0 (0.0%)	6 (66.7%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	7 (70.0%)
Total	**0 (0.0%)**	**0 (0.0%)**	**9 (90.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (10.0%)**	**10 (100.0%)**

[1]Where subjects have more than one SAE, only the highest category has been reported

Table 2. 28 - CHRONOS B: Number of Serious Adverse Events by Causality Relationship to event, by Treatment Arm

	Subjects with at least one SAEs[1]						
Causal Relationship	**Definitely**	**Probably**	**Possibly**	**Unlikely**	**Not related**	**Not assessable**	**Total**
Treatment							
Focal alone	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (25.0%)	0 (0.0%)	3 (50.0%)
Focal + finasteride	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Focal + bicalutamide	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (75.0%)	0 (0.0%)	3 (50.0%)
All subjects	**1 (16.7%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (16.7%)**	**4 (66.7%)**	**0 (0.0%)**	**6 (100.0%)**

	All SAEs (patients could have had more than one SAE)						
Causal Relationship	**Definitely**	**Probably**	**Possibly**	**Unlikely**	**Not related**	**Not assessable**	**Total**
Treatment							
Focal alone	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (12.5%)	0 (0.0%)	3 (30.0%)
Focal + finasteride	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Focal + bicalutamide	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (87.5%)	0 (0.0%)	7 (70.0%)
Total	**1 (10.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (10.0%)**	**8 (80.0%)**	**0 (0.0%)**	**10 (100.0%)**

[1]Where subjects have more than one SAE, only the highest relationship has been reported

8.4. Analysis of Secondary End Points

Table 3. 1: (Visit 1) - Summary statistics of EQ-5D-5L[1] dimensions and levels[2], by treatment arm (CHRONOS-A)

Focal					
Statistics	**Mobility n=18**	**Self-care n=18**	**Usual activities n=18**	**Pain/discomfort n=18**	**Anxiety/depression n=18**
Level 1	10 (55.6%)	13 (72.2%)	11 (61.1%)	6 (33.3%)	7 (38.9%)
Level 2	2 (11.1%)	0 (0.0%)	2 (11.1%)	6 (33.3%)	4 (22.2%)
Level 3	0 (0.0%)	1 (5.6%)	1 (5.6%)	0 (0.0%)	1 (5.6%)
Level 4	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Level 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	2 (11.1%)
Missing from eCRF – n (%)	5 (27.8%)	4 (22.2%)	4 (22.2%)	5 (27.8%)	4 (22.2%)
Radical					
Statistics	**Mobility n=18**	**Self-care n=18**	**Usual activities n=18**	**Pain/discomfort n=18**	**Anxiety/depression n=18**
Level 1	6 (33.3%)	6 (33.3%)	6 (33.3%)	5 (27.8%)	2 (11.1%)
Level 2	2 (11.1%)	2 (11.1%)	1 (5.6%)	2 (11.1%)	5 (27.8%)
Level 3	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (5.6%)	1 (5.6%)
Level 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Level 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing from eCRF – n (%)	10 (55.6%)	10 (55.6%)	10 (55.6%)	10 (55.6%)	10 (55.6%)

[1]See Section 6.2 for details
[2]Levels: Level 1 – None, Level 2 – Slight, Level 3 – Moderate, Level 4 – Severe and Level 5 – Extreme

Table 3. 2:(Visit 3) - Summary statistics of EQ-5D-5L[1] dimensions and levels[2], by treatment arm (CHRONOS-A)

Focal					
Statistics	**Mobility n=17**	**Self-care n=17**	**Usual activities n=17**	**Pain/discomfort n=17**	**Anxiety/depression n=17**
Level 1	6 (35.3%)	8 (47.1%)	8 (47.1%)	3 (17.6%)	6 (35.3%)
Level 2	2 (11.8%)	1 (5.9%)	1 (5.9%)	5 (29.4%)	2 (11.8%)
Level 3	1 (5.9%)	0 (0.0%)	1 (5.9%)	2 (11.8%)	2 (11.8%)
Level 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Level 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing from eCRF – n (%)	8 (47.1%)	8 (47.1%)	7 (41.2%)	7 (41.2%)	7 (41.2%)
Radical					
Statistics	**Mobility n=13**	**Self-care n=13**	**Usual activities n=13**	**Pain/discomfort n=13**	**Anxiety/depression n=13**
Level 1	4 (30.8%)	7 (53.8%)	2 (15.4%)	4 (30.8%)	3 (23.1%)
Level 2	1 (7.7%)	0 (0.0%)	4 (30.8%)	3 (23.1%)	4 (30.8%)
Level 3	2 (15.4%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Level 4	1 (7.7%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)
Level 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing from eCRF – n (%)	5 (38.5%)	5 (38.5%)	6 (46.2%)	5 (38.5%)	5 (38.5%)

[1]See Section 6.2 for details
[2]Levels: Level 1 – None, Level 2 – Slight, Level 3 – Moderate, Level 4 – Severe and Level 5 – Extreme

Table 3. 3: (Visit1) - Summary statistics for EQ VAS (EQ-5D-5L)[1], by treatment arm (CHRONOS-A)

	Statistics	Focal N=18	Radical N=18	Total N=36
EQ VAS (EQ-5D-5L)	N	13	8	21
	Min	30	45	30
	Mean (SD)	79.23 (15.79)	73.13 (18.11)	76.9 (16.54)
	Median (IQR)	85 (80 to 85)	77.5 (60 to 82.5)	80 (75 to 85)
	Max	90	100	100
	Missing from eCRF – n (%)	5 (27.8%)	10 (55.6%)	15 (41.7%)

[1]See Section 6.3 for details

Table 3. 4: (Visit3) - Summary statistics for EQ VAS (EQ-5D-5L)[1], by treatment arm (CHRONOS-A)

	Statistics	Focal N=17	Radical N=13	Total N=30
EQ VAS (EQ-5D-5L)	N	9	7	16
	Min	45	20	20
	Mean (SD)	73.11 (16.72)	59.29 (22.07)	67.06 (19.85)
	Median (IQR)	80 (65 to 85)	65 (40 to 80)	70 (55 to 82.5)
	Max	90	80	90
	Missing from eCRF – n (%)	8 (47.1%)	6 (46.2%)	14 (46.7%)

[1]See Section 6.3 for details

Table 3. 5: (Visit1) - Summary statistics of IIEF15[1] domains, by treatment arm (CHRONOS-A)

IIEF15 Domains	Statistics	Focal N=18	Radical N=18	Total N=36
Erectile Function	N	12	6	18
	Min	1	1	1
	Mean (SD)	10.42 (9.49)	6.5 (5.75)	9.11 (8.46)
	Median (IQR)	9 (1.5 to 17.5)	5 (1 to 13)	5.5 (1 to 14)
	Max	25	14	25
	Ungradable – n (%)	1 (5.6%)	2 (11.1%)	3 (8.3%)
	Missing from eCRF – n (%)	5 (27.8%)	10 (55.6%)	15 (41.7%)
Orgasmic Function	N	11	7	18
	Min	1	1	1
	Mean (SD)	5.18 (4)	3.86 (2.97)	4.67 (3.6)
	Median (IQR)	5 (1 to 10)	3 (1 to 6)	4 (1 to 9)
	Max	10	9	10
	Ungradable – n (%)	2 (11.1%)	1 (5.6%)	3 (8.3%)
	Missing from eCRF – n (%)	5 (27.8%)	10 (55.6%)	15 (41.7%)
Sexual Desire	N	13	7	20
	Min	2	2	2
	Mean (SD)	5.31 (1.93)	4.71 (1.89)	5.1 (1.89)
	Median (IQR)	6 (4 to 6)	4 (4 to 6)	6 (4 to 6)
	Max	8	8	8
	Ungradable – n (%)	0 (0.0%)	1 (5.6%)	1 (2.8%)
	Missing from eCRF – n (%)	5 (27.8%)	10 (55.6%)	15 (41.7%)
Intercourse Satisfaction	N	12	8	20
	Min	0	0	0
	Mean (SD)	3.92 (5.93)	3.13 (4.49)	3.6 (5.29)
	Median (IQR)	0 (0 to 10)	1.5 (0 to 4.5)	0 (0 to 7)
	Max	15	13	15
	Ungradable – n (%)	1 (5.6%)	0 (0.0%)	1 (2.8%)
	Missing from eCRF – n (%)	5 (27.8%)	10 (55.6%)	15 (41.7%)
Overall Satisfaction	N	11	7	18
	Min	2	2	2
	Mean (SD)	6.45 (3.17)	5.14 (3.24)	5.94 (3.17)
	Median (IQR)	8 (3 to 9)	5 (2 to 9)	5.5 (3 to 9)
	Max	10	10	10
	Ungradable – n (%)	2 (11.1%)	1 (5.6%)	3 (8.3%)
	Missing from eCRF – n (%)	5 (27.8%)	10 (55.6%)	15 (41.7%)

[1]See Section 6.4 for details

Table 3. 6: (Visit3) - Summary statistics of IIEF15[1] domains, by treatment arm (CHRONOS-A)

IIEF15 Domains	Statistics	Focal N=17	Radical N=13	Total N=30
Erectile Function	N	8	7	15
	Min	1	1	1
	Mean (SD)	10.75 (9.15)	2 (1.91)	6.67 (7.99)
	Median (IQR)	12 (2 to 14.5)	1 (1 to 3)	3 (1 to 13)
	Max	28	6	28
	Ungradable – n (%)	1 (5.9%)	0 (0.0%)	1 (3.3%)
	Missing from eCRF – n (%)	8 (47.1%)	6 (46.2%)	14 (46.7%)
Orgasmic Function	N	9	5	14
	Min	1	1	1
	Mean (SD)	5.56 (3.54)	2.2 (1.64)	4.36 (3.37)
	Median (IQR)	8 (2 to 8)	1 (1 to 4)	4 (1 to 8)
	Max	10	4	10
	Ungradable – n (%)	0 (0.0%)	2 (15.4%)	2 (6.7%)
	Missing from eCRF – n (%)	8 (47.1%)	6 (46.2%)	14 (46.7%)
Sexual Desire	N	9	7	16
	Min	2	2	2
	Mean (SD)	5.22 (2.49)	2.57 (0.79)	4.06 (2.32)
	Median (IQR)	6 (3 to 7)	2 (2 to 3)	3 (2 to 6.5)
	Max	8	4	8
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	8 (47.1%)	6 (46.2%)	14 (46.7%)
Intercourse Satisfaction	N	9	7	16
	Min	0	0	0
	Mean (SD)	4.11 (5.25)	0.29 (0.76)	2.44 (4.34)
	Median (IQR)	0 (0 to 8)	0 (0 to 0)	0 (0 to 4.5)
	Max	14	2	14
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	8 (47.1%)	6 (46.2%)	14 (46.7%)
Overall Satisfaction	N	7	7	14
	Min	2	2	2
	Mean (SD)	5.86 (2.61)	3.43 (2.15)	4.64 (2.62)
	Median (IQR)	6 (4 to 8)	3 (2 to 4)	4 (2 to 6)
	Max	10	8	10
	Ungradable – n (%)	2 (11.8%)	0 (0.0%)	2 (6.7%)
	Missing from eCRF – n (%)	8 (47.1%)	6 (46.2%)	14 (46.7%)

[1]See Section 6.4 for details

Table 3. 7: (Visit1) - Summary statistics of EPIC-26[1] domains, by treatment arm (CHRONOS-A)

EPIC-26 Domains	Statistics	Focal N=18	Radical N=18	Total N=36
Urinary Incontinence	N	13	8	21
	Min	58.25	37.5	37.5
	Mean (SD)	90.1 (12.54)	86.75 (21.42)	88.82 (16.05)
	Median (IQR)	91.75 (85.5 to 100)	95.88 (82.38 to 100)	91.75 (85.5 to 100)
	Max	100	100	100
	Ungradable – n (%)	1 (5.6%)	0 (0.0%)	1 (2.8%)
	Missing from eCRF – n (%)	4 (22.2%)	10 (55.6%)	14 (38.9%)
Urinary Irritative/ Obstructive	N	11	7	18
	Min	62.5	56.25	56.25
	Mean (SD)	82.39 (10.39)	84.82 (14.82)	83.33 (11.94)
	Median (IQR)	81.25 (75 to 87.5)	87.5 (75 to 93.75)	87.5 (75 to 93.75)
	Max	100	100	100
	Ungradable – n (%)	3 (16.7%)	1 (5.6%)	4 (11.1%)
	Missing from eCRF – n (%)	4 (22.2%)	10 (55.6%)	14 (38.9%)
Bowel	N	14	8	22
	Min	16.67	79.17	16.67
	Mean (SD)	87.5 (22.88)	95.31 (8.75)	90.34 (19.09)
	Median (IQR)	100 (83.33 to 100)	100 (91.67 to 100)	100 (83.33 to 100)
	Max	100	100	100
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	4 (22.2%)	10 (55.6%)	14 (38.9%)
Sexual	N	12	7	19
	Min	0	0	0
	Mean (SD)	52.08 (31.24)	26.62 (33.84)	42.7 (33.72)
	Median (IQR)	67.28 (17.33 to 77.08)	13.83 (8.33 to 27.83)	27.83 (13.83 to 75)
	Max	83.3	100	100
	Ungradable – n (%)	2 (11.1%)	1 (5.6%)	3 (8.3%)
	Missing from eCRF – n (%)	4 (22.2%)	10 (55.6%)	14 (38.9%)
Hormonal	N	14	6	20
	Min	60	40	40
	Mean (SD)	86.43 (13.36)	85 (22.58)	86 (16.03)
	Median (IQR)	90 (75 to 100)	90 (90 to 100)	90 (77.5 to 100)
	Max	100	100	100
	Ungradable – n (%)	0 (0.0%)	2 (11.1%)	2 (5.6%)
	Missing from eCRF – n (%)	4 (22.2%)	10 (55.6%)	14 (38.9%)

[1]See Section 6.5 for details

Table 3. 8: (Visit3) - Summary statistics of EPIC-26[1] domains, by treatment arm (CHRONOS-A)

EPIC-26 Domains	Statistics	Focal N=17	Radical N=13	Total N=30
Urinary Incontinence	N	7	6	13
	Min	79.25	60.5	60.5
	Mean (SD)	89.93 (9.76)	78.88 (14.91)	84.83 (13.16)
	Median (IQR)	85.5 (79.25 to 100)	77.13 (66.75 to 91.75)	85.5 (79.25 to 100)
	Max	100	100	100
	Ungradable – n (%)	3 (17.6%)	2 (15.4%)	5 (16.7%)
	Missing from eCRF – n (%)	7 (41.2%)	5 (38.5%)	12 (40%)
Urinary Irritative/ Obstructive	N	7	6	13
	Min	31.25	43.75	31.25
	Mean (SD)	77.68 (22.49)	63.54 (20.7)	71.15 (22.03)
	Median (IQR)	81.25 (75 to 93.75)	62.5 (43.75 to 68.75)	75 (62.5 to 87.5)
	Max	100	100	100
	Ungradable – n (%)	3 (17.6%)	2 (15.4%)	5 (16.7%)
	Missing from eCRF – n (%)	7 (41.2%)	5 (38.5%)	12 (40%)
Bowel	N	10	7	17
	Min	79.17	58.33	58.33
	Mean (SD)	95.42 (7.2)	82.14 (16.79)	89.95 (13.43)
	Median (IQR)	100 (91.67 to 100)	79.17 (66.67 to 100)	95.83 (79.17 to 100)
	Max	100	100	100
	Ungradable – n (%)	0 (0.0%)	1 (7.7%)	1 (3.3%)
	Missing from eCRF – n (%)	7 (41.2%)	5 (38.5%)	12 (40%)
Sexual	N	10	7	17
	Min	16.67	0	0
	Mean (SD)	49.47 (27.3)	13.29 (13.25)	34.57 (28.67)
	Median (IQR)	53.5 (22.17 to 73.67)	12.5 (0 to 16.67)	22.17 (16.67 to 54.17)
	Max	91.67	38.83	91.67
	Ungradable – n (%)	0 (0.0%)	1 (7.7%)	1 (3.3%)
	Missing from eCRF – n (%)	7 (41.2%)	5 (38.5%)	12 (40%)
Hormonal	N	9	8	17
	Min	50	25	25
	Mean (SD)	87.78 (17.34)	68.75 (24.31)	78.82 (22.47)
	Median (IQR)	100 (80 to 100)	72.5 (55 to 85)	85 (60 to 100)
	Max	100	100	100
	Ungradable – n (%)	1 (5.9%)	0 (0.0%)	1 (3.3%)
	Missing from eCRF – n (%)	7 (41.2%)	5 (38.5%)	12 (40%)

[1]See Section 6.5 for details

Table 3. 9: (Visit1) - Summary statistics of EPIC-URINARY DOMAIN[1] subscales, by treatment arm (CHRONOS-A)

EPIC-URINARY DOMAIN subscales	Statistics	Focal N=18	Radical N=18	Total N=36
Function	N	14	8	22
	Min	66.6	70	66.6
	Mean (SD)	91.69 (9.42)	91.28 (10.27)	91.54 (9.49)
	Median (IQR)	93.4 (88.4 to 100)	93.4 (86.7 to 100)	93.4 (88.4 to 100)
	Max	100	100	100
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	4 (22.2%)	10 (55.6%)	14 (38.9%)
Bother	N	14	8	22
	Min	50	32.14	32.14
	Mean (SD)	75.34 (14.48)	76.49 (18.95)	75.76 (15.8)
	Median (IQR)	73.21 (64.29 to 89.29)	82.14 (75 to 86.31)	78.57 (67.86 to 89.29)
	Max	96.429	92.857	96.429
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	4 (22.2%)	10 (55.6%)	14 (38.9%)
Incontinence	N	14	8	22
	Min	52	37.5	37.5
	Mean (SD)	87.38 (15.77)	86.75 (21.42)	87.15 (17.52)
	Median (IQR)	91.75 (79.25 to 100)	95.88 (82.38 to 100)	91.75 (79.25 to 100)
	Max	100	100	100
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	4 (22.2%)	10 (55.6%)	14 (38.9%)
Irritative/ Obstructive	N	14	8	22
	Min	70.83	60.71	60.71
	Mean (SD)	81.34 (9.36)	81.99 (11.93)	81.57 (10.09)
	Median (IQR)	78.57 (71.43 to 89.29)	82.14 (75 to 92.26)	80.36 (71.43 to 91.67)
	Max	96.43	96.43	96.43
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	4 (22.2%)	10 (55.6%)	14 (38.9%)
Urinary Summary	N	14	8	22
	Min	63.17	47.92	47.92
	Mean (SD)	82.23 (10.94)	82.7 (14.8)	82.4 (12.13)
	Median (IQR)	84.38 (72.25 to 89.58)	87.37 (82.29 to 89.25)	86.13 (78.5 to 89.58)
	Max	97.92	95.83	97.92
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	4 (22.2%)	10 (55.6%)	14 (38.9%)
EPIC-Urinary (Q5, Pad usage) – n (%)	None	14 (77.8%)	7 (38.9%)	21 (58.3%)
	1 per day	0 (0.0%)	1 (5.6%)	1 (2.8%)
	2 per day	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3+per day	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	4 (22.2%)	10 (55.6%)	14 (38.9%)

[1]See Section 6.5 for details

Table 3. 10: (Visit3) - Summary statistics of EPIC-URINARY DOMAIN[1] subscales, by treatment arm (CHRONOS-A)

EPIC-URINARY DOMAIN subscales	Statistics	Focal N=17	Radical N=13	Total N=30
Function	N	10	7	17
	Min	58.4	13.2	13.2
	Mean (SD)	88.54 (12.62)	77.4 (30.96)	83.95 (21.93)
	Median (IQR)	91.7 (88.4 to 95)	88.4 (63.4 to 100)	88.4 (83.4 to 95)
	Max	100	100	100
	Ungradable – n (%)	0 (0.0%)	1 (7.7%)	1 (3.3%)
	Missing from eCRF – n (%)	7 (41.2%)	6 (46.2%)	13 (43.3%)
Bother	N	10	6	16
	Min	25	35.71	25
	Mean (SD)	74.29 (20.4)	55.36 (16.71)	67.19 (20.79)
	Median (IQR)	75 (71.43 to 85.71)	53.57 (46.43 to 57.14)	71.43 (53.57 to 83.93)
	Max	96.43	85.71	96.43
	Ungradable – n (%)	0 (0.0%)	2 (15.4%)	2 (6.7%)
	Missing from eCRF – n (%)	7 (41.2%)	7 (53.8%)	14 (46.7%)
Incontinence	N	10	5	15
	Min	52.25	66.75	52.25
	Mean (SD)	83.18 (16.31)	82.15 (14.97)	82.83 (15.34)
	Median (IQR)	86.5 (79.25 to 100)	85.5 (66.75 to 91.75)	85.5 (66.75 to 100)
	Max	100	100	100
	Ungradable – n (%)	0 (0.0%)	3 (23.1%)	3 (10%)
	Missing from eCRF – n (%)	7 (41.2%)	8 (61.5%)	15 (50%)
Irritative/ Obstructive	N	10	6	16
	Min	28.57	50	28.57
	Mean (SD)	79.64 (19.57)	65.48 (15.92)	74.33 (19.09)
	Median (IQR)	85.71 (75 to 89.29)	64.29 (50 to 71.43)	78.57 (64.29 to 89.29)
	Max	96.43	92.86	96.43
	Ungradable – n (%)	0 (0.0%)	2 (15.4%)	2 (6.7%)
	Missing from eCRF – n (%)	7 (41.2%)	7 (53.8%)	14 (46.7%)
Urinary Summary	N	10	6	16
	Min	38.92	45	38.92
	Mean (SD)	80.23 (16.44)	66.08 (15.36)	74.92 (17.05)
	Median (IQR)	84.38 (74.33 to 91.67)	68.08 (53.5 to 72.92)	76.42 (68.08 to 88.21)
	Max	95.83	88.92	95.83
	Ungradable – n (%)	0 (0.0%)	2 (15.4%)	2 (6.7%)
	Missing from eCRF – n (%)	7 (41.2%)	7 (53.8%)	14 (46.7%)
EPIC-Urinary (Q5, Pad usage) – n (%)	None	9 (52.9%)	6 (46.2%)	15 (50.0%)
	1 per day	1 (5.9%)	1 (7.7%)	2 (6.7%)
	2 per day	0 (0.0%)	1 (7.7%)	1 (3.3%)
	3+per day	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	7 (41.2%)	5 (38.5%)	12 (40.0%)

[1]See Section 6.5 for details

Table 3. 11: (Visit1) - Summary statistics of EQ-5D-5L[1] dimensions and levels[2], by treatment arm (CHRONOS-B)

Focal + finasteride					
Statistics	**Mobility n=21**	**Self-care n=21**	**Usual activities n=21**	**Pain/discomfort n=21**	**Anxiety/depression n=21**
Level 1	17 (81.0%)	18 (85.7%)	16 (76.2%)	12 (57.1%)	14 (66.7%)
Level 2	1 (4.8%)	0 (0.0%)	2 (9.5%)	4 (19.0%)	3 (14.3%)
Level 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.5%)	1 (4.8%)
Level 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Level 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing from eCRF – n (%)	3 (14.3%)	3 (14.3%)	3 (14.3%)	3 (14.3%)	3 (14.3%)
Focal + bicalutamide					
Statistics	**Mobility n=21**	**Self-care n=21**	**Usual activities n=21**	**Pain/discomfort n=21**	**Anxiety/depression n=21**
Level 1	17 (81.0%)	20 (95.2%)	18 (85.7%)	11 (52.4%)	11 (52.4%)
Level 2	2 (9.5%)	0 (0.0%)	1 (4.8%)	7 (33.3%)	6 (28.6%)
Level 3	1 (4.8%)	0 (0.0%)	0 (0.0%)	2 (9.5%)	2 (9.5%)
Level 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (4.8%)
Level 5	0 (0.0%)	0 (0.0%)	1 (4.8%)	0 (0.0%)	0 (0.0%)
Missing from eCRF – n (%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)
Focal alone					
Statistics	**Mobility n=22**	**Self-care n=22**	**Usual activities n=22**	**Pain/discomfort n=22**	**Anxiety/depression n=22**
Level 1	17 (77.3%)	19 (86.4%)	15 (68.2%)	10 (45.5%)	8 (36.4%)
Level 2	2 (9.1%)	0 (0.0%)	3 (13.6%)	8 (36.4%)	8 (36.4%)
Level 3	0 (0.0%)	1 (4.5%)	1 (4.5%)	1 (4.5%)	3 (13.6%)
Level 4	1 (4.5%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)
Level 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)
Missing from eCRF – n (%)	2 (9.1%)	2 (9.1%)	2 (9.1%)	2 (9.1%)	2 (9.1%)

[1]See Section 6.2 for details
[2]Levels: Level 1 – None, Level 2 – Slight, Level 3 – Moderate, Level 4 – Severe and Level 5 – Extreme

Table 3. 12: (Visit3) - Summary statistics of EQ-5D-5L[1] dimensions and levels, by treatment arm (CHRONOS-B)

Focal + finasteride					
Statistics	**Mobility n=20**	**Self-care n=20**	**Usual activities n=20**	**Pain/discomfort n=20**	**Anxiety/depression n=20**
Level 1	15 (75.0%)	16 (80.0%)	15 (75.0%)	14 (70.0%)	11 (55.0%)
Level 2	1 (5.0%)	1 (5.0%)	0 (0.0%)	2 (10.0%)	5 (25.0%)
Level 3	2 (10.0%)	0 (0.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)
Level 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (5.0%)
Level 5	0 (0.0%)	0 (0.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)
Missing from eCRF – n (%)	2 (10.0%)	3 (15.0%)	2 (10.0%)	2 (10.0%)	2 (10.0%)
Focal + bicalutamide					
Statistics	**Mobility n=20**	**Self-care n=20**	**Usual activities n=20**	**Pain/discomfort n=20**	**Anxiety/depression n=20**
Level 1	8 (40.0%)	15 (75.0%)	12 (60.0%)	6 (30.0%)	11 (55.0%)
Level 2	6 (30.0%)	1 (5.0%)	3 (15.0%)	6 (30.0%)	3 (15.0%)
Level 3	2 (10.0%)	0 (0.0%)	1 (5.0%)	4 (20.0%)	2 (10.0%)
Level 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Level 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing from eCRF – n (%)	4 (20.0%)	4 (20.0%)	4 (20.0%)	4 (20.0%)	4 (20.0%)
Focal alone					
Statistics	**Mobility n=22**	**Self-care n=22**	**Usual activities n=22**	**Pain/discomfort n=22**	**Anxiety/depression n=22**
Level 1	10 (45.5%)	11 (50.0%)	9 (40.9%)	9 (40.9%)	7 (31.8%)
Level 2	2 (9.1%)	1 (4.5%)	2 (9.1%)	3 (13.6%)	5 (22.7%)
Level 3	0 (0.0%)	1 (4.5%)	1 (4.5%)	0 (0.0%)	1 (4.5%)
Level 4	1 (4.5%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)
Level 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing from eCRF – n (%)	9 (40.9%)	9 (40.9%)	9 (40.9%)	9 (40.9%)	9 (40.9%)

[1]See Section 6.2 for details
[2]Levels: Level 1 – None, Level 2 – Slight, Level 3 – Moderate, Level 4 – Severe and Level 5 – Extreme

Table 3. 13: (Visit4) - Summary statistics of EQ-5D-5L[1] dimensions and levels, by treatment arm (CHRONOS-B)

Focal + finasteride					
Statistics	**Mobility n=20**	**Self-care n=20**	**Usual activities n=20**	**Pain/discomfort n=20**	**Anxiety/depression n=20**
Level 1	10 (50.0%)	10 (50.0%)	10 (50.0%)	10 (50.0%)	7 (35.0%)
Level 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (10.0%)
Level 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
Level 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Level 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing from eCRF – n (%)	10 (50.0%)	10 (50.0%)	10 (50.0%)	10 (50.0%)	10 (50.0%)
Focal + bicalutamide					
Statistics	**Mobility n=21**	**Self-care n=21**	**Usual activities n=21**	**Pain/discomfort n=21**	**Anxiety/depression n=21**
Level 1	6 (28.6%)	9 (42.9%)	7 (33.3%)	3 (14.3%)	4 (19.0%)
Level 2	2 (9.5%)	0 (0.0%)	1 (4.8%)	3 (14.3%)	4 (19.0%)
Level 3	1 (4.8%)	0 (0.0%)	1 (4.8%)	3 (14.3%)	1 (4.8%)
Level 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Level 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing from eCRF – n (%)	12 (57.1%)	12 (57.1%)	12 (57.1%)	12 (57.1%)	12 (57.1%)
Focal alone					
Statistics	**Mobility n=22**	**Self-care n=22**	**Usual activities n=22**	**Pain/discomfort n=22**	**Anxiety/depression n=22**
Level 1	8 (36.4%)	13 (59.1%)	9 (40.9%)	5 (22.7%)	6 (27.3%)
Level 2	5 (22.7%)	0 (0.0%)	4 (18.2%)	7 (31.8%)	4 (18.2%)
Level 3	0 (0.0%)	1 (4.5%)	0 (0.0%)	1 (4.5%)	2 (9.1%)
Level 4	1 (4.5%)	0 (0.0%)	1 (4.5%)	2 (9.1%)	2 (9.1%)
Level 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)
Missing from eCRF – n (%)	8 (36.4%)	8 (36.4%)	8 (36.4%)	8 (36.4%)	8 (36.4%)

[1]See Section 6.2 for details
[2]Levels: Level 1 – None, Level 2 – Slight, Level 3 – Moderate, Level 4 – Severe and Level 5 – Extreme

Table 3. 14: (Visit1) - Summary statistics for EQ VAS (EQ-5D-5L)[1], by treatment arm (CHRONOS-B)

	Statistics	Focal + finasteride N=21	Focal + bicalutamide N=21	Focal alone N=22	Total N=64
EQ VAS (EQ-5D-5L)	N	17	20	20	57
	Min	23	25	25	23
	Mean (SD)	82.53 (17.28)	71.3 (21.92)	70.5 (19.46)	74.37 (20.14)
	Median (IQR)	85 (80 to 95)	75 (70 to 85)	75 (60 to 82.5)	80 (70 to 85)
	Max	100	99	95	100
	Missing from eCRF – n (%)	4 (19%)	1 (4.8%)	2 (9.1%)	7 (10.9%)

[1]See Section 6.3 for details

Table 3. 15: (Visit3) - Summary statistics for EQ VAS (EQ-5D-5L)[1], by treatment arm (CHRONOS-B)

	Statistics	Focal + finasteride N=20	Focal + bicalutamide N=20	Focal alone N=22	Total N=62
EQ VAS (EQ-5D-5L)	N	18	15	14	47
	Min	30	40	25	25
	Mean (SD)	80.56 (17.78)	72.47 (12.92)	77.71 (18.83)	77.13 (16.72)
	Median (IQR)	85 (80 to 90)	72 (70 to 80)	81.5 (75 to 90)	80 (70 to 90)
	Max	98	95	95	98
	Missing from eCRF – n (%)	2 (10%)	5 (25%)	8 (36.4%)	15 (24.2%)

[1]See Section 6.3 for details

Table 3. 16: (Visit4) - Summary statistics for EQ VAS (EQ-5D-5L)[1], by treatment arm (CHRONOS-B)

	Statistics	Focal + finasteride N=20	Focal + bicalutamide N=21	Focal alone N=22	Total N=63
EQ VAS (EQ-5D-5L)	N	11	9	14	34
	Min	42	50	30	30
	Mean (SD)	85.55 (15.58)	72.89 (12.85)	69.57 (20.4)	75.62 (18.11)
	Median (IQR)	90 (85 to 95)	75 (65 to 81)	73 (60 to 85)	80.5 (65 to 90)
	Max	100	90	98	100
	Missing from eCRF – n (%)	9 (45%)	12 (57.1%)	8 (36.4%)	29 (46%)

[1]See Section 6.3 for details

Table 3. 17: (Visit1) - Summary statistics of IIEF15[1] domains, by treatment arm (CHRONOS-B)

IIEF15 Domains	Statistics	Focal + finasteride N=21	Focal + bicalutamide N=21	Focal alone N=22	Total N=64
Erectile Function	N	17	17	18	52
	Min	3	1	1	1
	Mean (SD)	21.29 (8.27)	15.53 (11.12)	15.94 (11.71)	17.56 (10.63)
	Median (IQR)	22 (15 to 29)	15 (5 to 28)	15 (4 to 29)	19.5 (6.5 to 28)
	Max	30	29	30	30
	Ungradable – n (%)	0 (0.0%)	2 (9.5%)	1 (4.5%)	3 (4.7%)
	Missing from eCRF – n (%)	4 (19%)	2 (9.5%)	3 (13.6%)	9 (14.1%)
Orgasmic Function	N	17	15	19	51
	Min	4	1	1	1
	Mean (SD)	8.59 (1.7)	7.2 (3.45)	7.11 (3.2)	7.63 (2.9)
	Median (IQR)	9 (8 to 10)	8 (5 to 10)	8 (6 to 10)	8 (6 to 10)
	Max	10	10	10	10
	Ungradable – n (%)	0 (0.0%)	4 (19%)	0 (0.0%)	4 (6.3%)
	Missing from eCRF – n (%)	4 (19%)	2 (9.5%)	3 (13.6%)	9 (14.1%)
Sexual Desire	N	17	17	19	53
	Min	3	3	2	2
	Mean (SD)	7.24 (2.02)	6 (1.77)	6.37 (2.41)	6.53 (2.12)
	Median (IQR)	7 (6 to 9)	7 (5 to 7)	6 (4 to 9)	7 (5 to 8)
	Max	10	8	10	10
	Ungradable – n (%)	0 (0.0%)	2 (9.5%)	0 (0.0%)	2 (3.1%)
	Missing from eCRF – n (%)	4 (19%)	2 (9.5%)	3 (13.6%)	9 (14.1%)
Intercourse Satisfaction	N	17	18	19	54
	Min	0	0	0	0
	Mean (SD)	7.53 (5.27)	5.56 (5.34)	6.05 (5.66)	6.35 (5.39)
	Median (IQR)	10 (0 to 12)	8 (0 to 9)	8 (0 to 11)	8.5 (0 to 11)
	Max	13	14	15	15
	Ungradable – n (%)	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (1.6%)
	Missing from eCRF – n (%)	4 (19%)	2 (9.5%)	3 (13.6%)	9 (14.1%)
Overall Satisfaction	N	15	18	18	51
	Min	2	2	2	2
	Mean (SD)	7.33 (2.69)	6.11 (2.7)	7 (2.7)	6.78 (2.69)
	Median (IQR)	8 (5 to 10)	6 (4 to 8)	7.5 (5 to 9)	7 (5 to 9)
	Max	10	10	10	10
	Ungradable – n (%)	2 (9.5%)	1 (4.8%)	1 (4.5%)	4 (6.3%)
	Missing from eCRF – n (%)	4 (19%)	2 (9.5%)	3 (13.6%)	9 (14.1%)

[1]See Section 6.4 for details

Table 3. 18: (Visit3) - Summary statistics of IIEF15[1] domains, by treatment arm (CHRONOS-B)

IIEF15 Domains	Statistics	Focal + finasteride N=20	Focal + bicalutamide N=20	Focal alone N=22	Total N=62
Erectile Function	N	18	15	13	46
	Min	1	1	1	1
	Mean (SD)	14.94 (10.71)	7.33 (6.3)	13.46 (10.89)	12.04 (9.93)
	Median (IQR)	13 (4 to 26)	5 (3 to 11)	13 (3 to 20)	9.5 (3 to 19)
	Max	30	24	30	30
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	1 (1.6%)
	Missing from eCRF – n (%)	2 (10%)	5 (25%)	8 (36.4%)	15 (24.2%)
Orgasmic Function	N	18	14	12	44
	Min	1	1	1	1
	Mean (SD)	6 (2.54)	4.43 (3.08)	5.67 (2.93)	5.41 (2.85)
	Median (IQR)	6 (4 to 8)	3.5 (2 to 6)	6 (4 to 7.5)	5.5 (3 to 8)
	Max	10	10	10	10
	Ungradable – n (%)	0 (0.0%)	1 (5%)	2 (9.1%)	3 (4.8%)
	Missing from eCRF – n (%)	2 (10%)	5 (25%)	8 (36.4%)	15 (24.2%)
Sexual Desire	N	18	14	11	43
	Min	2	2	2	2
	Mean (SD)	6.56 (1.98)	4.86 (1.66)	5.73 (2.65)	5.79 (2.16)
	Median (IQR)	6.5 (5 to 8)	4.5 (4 to 6)	6 (4 to 8)	6 (4 to 8)
	Max	10	8	9	10
	Ungradable – n (%)	0 (0.0%)	1 (5%)	3 (13.6%)	4 (6.5%)
	Missing from eCRF – n (%)	2 (10%)	5 (25%)	8 (36.4%)	15 (24.2%)
Intercourse Satisfaction	N	18	15	13	46
	Min	0	0	0	0
	Mean (SD)	5.89 (5.52)	2.93 (3.49)	5.15 (5.15)	4.72 (4.9)
	Median (IQR)	6.5 (0 to 10)	2 (0 to 5)	4 (0 to 9)	3.5 (0 to 9)
	Max	15	10	13	15
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	1 (1.6%)
	Missing from eCRF – n (%)	2 (10%)	5 (25%)	8 (36.4%)	15 (24.2%)
Overall Satisfaction	N	16	14	11	41
	Min	2	2	2	2
	Mean (SD)	5.94 (3.19)	3.79 (2.08)	5.82 (2.23)	5.17 (2.74)
	Median (IQR)	6 (2 to 8.5)	3 (2 to 6)	6 (4 to 7)	6 (2 to 7)
	Max	10	8	10	10
	Ungradable – n (%)	2 (10%)	1 (5%)	3 (13.6%)	6 (9.7%)
	Missing from eCRF – n (%)	2 (10%)	5 (25%)	8 (36.4%)	15 (24.2%)

[1]See Section 6.4 for details

Table 3. 19: (Visit4) - Summary statistics of IIEF15[1] domains, by treatment arm (CHRONOS-B)

IIEF15 Domains	Statistics	Focal + finasteride N=20	Focal + bicalutamide N=21	Focal alone N=22	Total N=63
Erectile Function	N	10	9	14	33
	Min	3	1	1	1
	Mean (SD)	21.4 (8.85)	8.89 (10.89)	14.93 (10.57)	15.24 (10.97)
	Median (IQR)	22.5 (19 to 29)	2 (1 to 16)	15.5 (5 to 23)	16 (3 to 24)
	Max	30	28	30	30
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	10 (50%)	12 (57.1%)	8 (36.4%)	30 (47.6%)
Orgasmic Function	N	9	8	14	31
	Min	3	1	1	1
	Mean (SD)	7.22 (2.59)	4.5 (4.04)	5.29 (2.95)	5.65 (3.24)
	Median (IQR)	8 (7 to 8)	3.5 (1 to 8)	4.5 (4 to 8)	6 (3 to 8)
	Max	10	10	10	10
	Ungradable – n (%)	1 (5%)	1 (4.8%)	0 (0.0%)	2 (3.2%)
	Missing from eCRF – n (%)	10 (50%)	12 (57.1%)	8 (36.4%)	30 (47.6%)
Sexual Desire	N	10	9	14	33
	Min	4	2	2	2
	Mean (SD)	7.4 (2.12)	4.89 (2.52)	5.64 (2.79)	5.97 (2.65)
	Median (IQR)	7.5 (6 to 9)	5 (2 to 7)	5.5 (3 to 8)	6 (4 to 8)
	Max	10	8	10	10
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	10 (50%)	12 (57.1%)	8 (36.4%)	30 (47.6%)
Intercourse Satisfaction	N	10	9	14	33
	Min	0	0	0	0
	Mean (SD)	8.6 (4.77)	4.11 (5.28)	6.71 (5.38)	6.58 (5.3)
	Median (IQR)	9.5 (8 to 12)	2 (0 to 7)	8.5 (0 to 12)	8 (0 to 12)
	Max	15	13	13	15
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	10 (50%)	12 (57.1%)	8 (36.4%)	30 (47.6%)
Overall Satisfaction	N	9	8	13	30
	Min	2	2	2	2
	Mean (SD)	7.44 (2.65)	5 (2.67)	5.92 (3.09)	6.13 (2.92)
	Median (IQR)	8 (7 to 10)	5 (2.5 to 7)	7 (2 to 8)	7 (3 to 8)
	Max	10	9	10	10
	Ungradable – n (%)	1 (5%)	1 (4.8%)	1 (4.5%)	3 (4.8%)
	Missing from eCRF – n (%)	10 (50%)	12 (57.1%)	8 (36.4%)	30 (47.6%)

[1]See Section 6.4 for details

Table 3. 20: (Visit1) - Summary statistics of EPIC-26[1] domains, by treatment arm (CHRONOS-B)

EPIC-26 Domains	Statistics	Focal + finasteride N=21	Focal + bicalutamide N=21	Focal alone N=22	Total N=64
Urinary Incontinence	N	17	19	17	53
	Min	22.75	58.5	33.25	22.75
	Mean (SD)	80.68 (21.16)	89.95 (15.52)	82.38 (21.1)	84.55 (19.37)
	Median (IQR)	85.5 (73 to 100)	100 (73 to 100)	91.75 (79.25 to 100)	91.75 (73 to 100)
	Max	100	100	100	100
	Ungradable – n (%)	1 (4.8%)	1 (4.8%)	2 (9.1%)	4 (6.3%)
	Missing from eCRF – n (%)	3 (14.3%)	1 (4.8%)	3 (13.6%)	7 (10.9%)
Urinary Irritative/ Obstructive	N	17	17	17	51
	Min	50	37.5	37.5	37.5
	Mean (SD)	82.72 (15.23)	80.15 (15.82)	81.99 (20.12)	81.62 (16.88)
	Median (IQR)	87.5 (68.75 to 93.75)	81.25 (75 to 87.5)	87.5 (68.75 to 100)	87.5 (68.75 to 93.75)
	Max	100	100	100	100
	Ungradable – n (%)	1 (4.8%)	3 (14.3%)	2 (9.1%)	6 (9.4%)
	Missing from eCRF – n (%)	3 (14.3%)	1 (4.8%)	3 (13.6%)	7 (10.9%)
Bowel	N	18	19	18	55
	Min	66.67	37.50	62.50	37.50
	Mean (SD)	92.59 (11.21)	91.01 (15.23)	90.97 (12.72)	91.52 (12.98)
	Median (IQR)	100 (87.5 to 100)	100 (87.5 to 100)	95.83 (83.33 to 100)	100 (87.5 to 100)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	1 (4.8%)	1 (4.5%)	2 (3.1%)
	Missing from eCRF – n (%)	3 (14.3%)	1 (4.8%)	3 (13.6%)	7 (10.9%)
Sexual	N	18	19	19	56
	Min	9.67	0.00	13.83	0.00
	Mean (SD)	75.16 (26.16)	58.71 (30.72)	61.71 (29.28)	65.01 (29.19)
	Median (IQR)	83.33 (61.17 to 100)	62.5 (32 to 79.17)	62.5 (40.33 to 90)	68.08 (45.83 to 91.67)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (1.6%)
	Missing from eCRF – n (%)	3 (14.3%)	1 (4.8%)	3 (13.6%)	7 (10.9%)
Hormonal	N	18	17	19	54
	Min	70	75	40	40
	Mean (SD)	94.72 (8.99)	90.29 (9.6)	85.53 (15.63)	90.09 (12.3)
	Median (IQR)	100 (90 to 100)	90 (85 to 100)	90 (80 to 100)	95 (85 to 100)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	3 (14.3%)	0 (0.0%)	3 (4.7%)
	Missing from eCRF – n (%)	3 (14.3%)	1 (4.8%)	3 (13.6%)	7 (10.9%)

[1]See Section 6.4 for details

Table 3. 21: (Visit3) - Summary statistics of EPIC-26[1] domains, by treatment arm (CHRONOS-B)

EPIC-26 Domains	Statistics	Focal + finasteride N=20	Focal + bicalutamide N=20	Focal alone N=22	Total N=62
Urinary Incontinence	N	18	16	12	46
	Min	45.75	39.75	46	39.75
	Mean (SD)	81.76 (19.04)	83.77 (22.5)	84.25 (20.34)	83.11 (20.2)
	Median (IQR)	85.5 (66.75 to 100)	96.88 (60.5 to 100)	95.88 (63.63 to 100)	92.75 (60.5 to 100)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	2 (9.1%)	2 (3.2%)
	Missing from eCRF – n (%)	2 (10%)	4 (20%)	8 (36.4%)	14 (22.6%)
Urinary Irritative/ Obstructive	N	18	15	12	45
	Min	37.5	56.25	62.5	37.5
	Mean (SD)	81.6 (17.48)	84.58 (10.79)	88.02 (12.91)	84.31 (14.27)
	Median (IQR)	87.5 (68.75 to 93.75)	87.5 (81.25 to 93.75)	90.63 (78.13 to 100)	87.5 (81.25 to 93.75)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	1 (5%)	2 (9.1%)	3 (4.8%)
	Missing from eCRF – n (%)	2 (10%)	4 (20%)	8 (36.4%)	14 (22.6%)
Bowel	N	18	15	13	46
	Min	66.66666412	62.5	83.33333588	62.5
	Mean (SD)	95.05 (9.11)	94.72 (10.62)	96.47 (5.6)	95.34 (8.68)
	Median (IQR)	100 (91.67 to 100)	100 (91.67 to 100)	100 (95.83 to 100)	100 (91.67 to 100)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	1 (5%)	1 (4.5%)	2 (3.2%)
	Missing from eCRF – n (%)	2 (10%)	4 (20%)	8 (36.4%)	14 (22.6%)
Sexual	N	18	16	12	46
	Min	4.166666508	0	0	0
	Mean (SD)	53.07 (28.12)	25.07 (21.86)	50.36 (27.71)	42.63 (28.54)
	Median (IQR)	61.83 (26.33 to 75)	24.25 (7.58 to 34.08)	53.5 (35.42 to 65.33)	37.5 (18 to 62.5)
	Max	91.66666412	87.5	100	100
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	2 (9.1%)	2 (3.2%)
	Missing from eCRF – n (%)	2 (10%)	4 (20%)	8 (36.4%)	14 (22.6%)
Hormonal	N	17	15	12	44
	Min	45	40	60	40
	Mean (SD)	85.29 (20.58)	84.33 (15.45)	88.33 (13.03)	85.8 (16.77)
	Median (IQR)	100 (75 to 100)	85 (80 to 95)	92.5 (77.5 to 100)	90 (77.5 to 100)
	Max	100	100	100	100
	Ungradable – n (%)	1 (5%)	1 (5%)	2 (9.1%)	4 (6.5%)
	Missing from eCRF – n (%)	2 (10%)	4 (20%)	8 (36.4%)	14 (22.6%)

[1]See Section 6.4 for details

Table 3. 22: (Visit4) - Summary statistics of EPIC-26[1] domains, by treatment arm (CHRONOS-B)

EPIC-26 Domains	Statistics	Focal + finasteride N=20	Focal + bicalutamide N=21	Focal alone N=22	Total N=63
Urinary Incontinence	N	11	9	13	33
	Min	68.75	43.75	52.25	43.75
	Mean (SD)	90.18 (12.23)	87.31 (17.51)	91.87 (15.08)	90.06 (14.56)
	Median (IQR)	100 (79.25 to 100)	91.75 (85.5 to 100)	100 (91.75 to 100)	100 (85.5 to 100)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	9 (45%)	12 (57.1%)	9 (40.9%)	30 (47.6%)
Urinary Irritative/ Obstructive	N	11	8	13	32
	Min	81.25	50	43.75	43.75
	Mean (SD)	94.32 (7.1)	84.38 (19.48)	87.02 (17.01)	88.87 (15.2)
	Median (IQR)	100 (87.5 to 100)	90.63 (71.88 to 100)	93.75 (87.5 to 100)	93.75 (84.38 to 100)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (1.6%)
	Missing from eCRF – n (%)	9 (45%)	12 (57.1%)	9 (40.9%)	30 (47.6%)
Bowel	N	11	9	13	33
	Min	95.83	45.83	66.67	45.83
	Mean (SD)	98.86 (1.95)	87.5 (19.21)	95.19 (9.14)	94.32 (12.05)
	Median (IQR)	100 (95.83 to 100)	95.83 (83.33 to 100)	100 (95.83 to 100)	100 (95.83 to 100)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	9 (45%)	12 (57.1%)	9 (40.9%)	30 (47.6%)
Sexual	N	11	9	12	32
	Min	5.5	0	0	0
	Mean (SD)	70.83 (25.52)	29.8 (32.79)	57.08 (30.85)	54.13 (33.16)
	Median (IQR)	79.17 (66.6 to 91.67)	16.67 (4.17 to 44.5)	57 (34.08 to 87.5)	59.08 (27.08 to 83.33)
	Max	95.8	87.5	100	100
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	1 (1.6%)
	Missing from eCRF – n (%)	9 (45%)	12 (57.1%)	9 (40.9%)	30 (47.6%)
Hormonal	N	11	8	12	31
	Min	60	40	45	40
	Mean (SD)	91.36 (12.47)	84.38 (20.95)	88.33 (16.28)	88.39 (16.09)
	Median (IQR)	95 (85 to 100)	92.5 (75 to 100)	95 (85 to 100)	95 (85 to 100)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	1 (4.8%)	1 (4.5%)	2 (3.2%)
	Missing from eCRF – n (%)	9 (45%)	12 (57.1%)	9 (40.9%)	30 (47.6%)

[1]See Section 6.5 for details

Table 3. 23: (Visit1) - Summary statistics of EPIC-URINARY DOMAIN[1] subscales, by treatment arm (CHRONOS-B)

EPIC-URINARY DOMAIN subscales	Statistics	Focal + finasteride N=21	Focal + bicalutamide N=21	Focal alone N=22	Total N=64
Function	N	17	19	20	56
	Min	36.80	68.40	58.40	36.80
	Mean (SD)	89.34 (16.98)	91.17 (11.9)	90.19 (12.76)	90.26 (13.68)
	Median (IQR)	100 (85 to 100)	100 (78.4 to 100)	94.2 (85.9 to 100)	97.5 (84.2 to 100)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (1.6%)
	Missing from eCRF – n (%)	4 (19%)	2 (9.5%)	2 (9.1%)	8 (12.5%)
Bother	N	17	18	18	53
	Min	42.86	35.71	35.71	35.71
	Mean (SD)	77.52 (18.07)	77.81 (15.78)	78.17 (18.41)	77.84 (17.11)
	Median (IQR)	78.57 (60.71 to 92.86)	76.79 (67.86 to 91.67)	82.14 (67.86 to 92.86)	78.57 (67.86 to 92.86)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	2 (9.5%)	2 (9.1%)	4 (6.3%)
	Missing from eCRF – n (%)	4 (19%)	3 (14.3%)	4 (18.2%)	11 (17.2%)
Incontinence	N	17	19	18	54
	Min	48	48	33.25	33.25
	Mean (SD)	87.78 (17.5)	86.99 (18.08)	85.1 (21.52)	86.61 (18.8)
	Median (IQR)	100 (79.25 to 100)	100 (73 to 100)	100 (79.25 to 100)	100 (79.25 to 100)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	1 (4.8%)	2 (9.1%)	3 (4.7%)
	Missing from eCRF – n (%)	4 (19%)	2 (9.5%)	4 (18.2%)	10 (15.6%)
Irritative/ Obstructive	N	17	17	18	52
	Min	46.43	42.86	42.86	42.86
	Mean (SD)	81.09 (15.86)	83.19 (13.64)	83.53 (14.29)	82.62 (14.37)
	Median (IQR)	82.14 (75 to 92.86)	85.71 (82.14 to 89.29)	87.5 (75 to 92.86)	85.71 (75 to 92.86)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	3 (14.3%)	2 (9.1%)	5 (7.8%)
	Missing from eCRF – n (%)	4 (19%)	4 (19%)	4 (18.2%)	12 (18.8%)
Urinary Summary	N	17	19	18	54
	Min	57.00	49.33	45.17	45.17
	Mean (SD)	82.45 (14.37)	82.39 (12.3)	83 (15.68)	82.61 (13.88)
	Median (IQR)	82.67 (72.25 to 95.83)	79.55 (75 to 93.75)	85.79 (72.25 to 95.83)	83.33 (74.33 to 95.83)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	1 (4.8%)	2 (9.1%)	3 (4.7%)
	Missing from eCRF – n (%)	4 (19%)	2 (9.5%)	4 (18.2%)	10 (15.6%)
EPIC-Urinary (Q5, Pad usage) – n (%)	None	16 (76.2%)	18 (85.7%)	20 (90.9%)	54 (84.4%)
	1 per day	1 (4.8%)	2 (9.5%)	0 (0.0%)	3 (4.7%)
	2 per day	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3+per day	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	4 (19.0%)	1 (4.8%)	2 (9.1%)	7 (10.9%)

[1]See Section 6.4 for details

Table 3. 24: (Visit3) - Summary statistics of EPIC-URINARY DOMAIN[1] subscales, by treatment arm (CHRONOS-B)

EPIC-URINARY DOMAIN subscales	Statistics	Focal + finasteride N=20	Focal + bicalutamide N=20	Focal alone N=22	Total N=62
Function	N	18	14	13	45
	Min	36.80	62.50	56.60	36.80
	Mean (SD)	84.11 (18.31)	87.11 (14.7)	87.32 (16.1)	85.97 (16.32)
	Median (IQR)	89.2 (71.8 to 100)	94.2 (71.8 to 100)	95 (76.8 to 100)	93.4 (73.4 to 100)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	1 (5%)	1 (4.5%)	2 (3.2%)
	Missing from eCRF – n (%)	2 (10%)	6 (30%)	9 (40.9%)	17 (27.4%)
Bother	N	18	14	14	46
	Min	28.57	57.14	60.71	28.57
	Mean (SD)	76.98 (20.14)	78.53 (12.78)	82.82 (13.7)	79.23 (16.15)
	Median (IQR)	82.14 (71.43 to 89.29)	78.57 (67.86 to 89.29)	85.71 (71.43 to 96.43)	82.14 (71.43 to 92.86)
	Max	100	95.83	100	100
	Ungradable – n (%)	0 (0.0%)	1 (5%)	0 (0.0%)	1 (1.6%)
	Missing from eCRF – n (%)	2 (10%)	6 (30%)	8 (36.4%)	16 (25.8%)
Incontinence	N	18	12	13	43
	Min	45.75	43.75	37.5	37.5
	Mean (SD)	82.57 (20.24)	84.58 (20.9)	84.63 (22.5)	83.76 (20.64)
	Median (IQR)	95.88 (60.5 to 100)	96.88 (63.63 to 100)	100 (66.75 to 100)	100 (60.5 to 100)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	3 (15%)	1 (4.5%)	4 (6.5%)
	Missing from eCRF – n (%)	2 (10%)	8 (40%)	9 (40.9%)	19 (30.6%)
Irritative/ Obstructive	N	18	13	13	44
	Min	35.71	64.29	67.86	35.71
	Mean (SD)	79.96 (17.63)	84.07 (10.06)	86.63 (11.37)	83.14 (13.98)
	Median (IQR)	87.5 (71.43 to 92.86)	85.71 (78.57 to 92.86)	89.29 (83.33 to 96.43)	87.5 (75 to 92.86)
	Max	100	96.43	100	100
	Ungradable – n (%)	0 (0.0%)	2 (10%)	1 (4.5%)	3 (4.8%)
	Missing from eCRF – n (%)	2 (10%)	7 (35%)	9 (40.9%)	18 (29%)
Urinary Summary	N	18	13	13	44
	Min	41.00	59.09	59.00	41.00
	Mean (SD)	79.95 (17.57)	83.44 (12.22)	84.76 (13.17)	82.4 (14.72)
	Median (IQR)	85.08 (74.33 to 93.75)	87.5 (75 to 93.75)	88.92 (77.08 to 95.17)	87.17 (74.67 to 93.75)
	Max	100	97.73	100	100
	Ungradable – n (%)	0 (0.0%)	2 (10%)	1 (4.5%)	3 (4.8%)
	Missing from eCRF – n (%)	2 (10%)	7 (35%)	9 (40.9%)	18 (29%)
EPIC-Urinary (Q5, Pad usage) – n (%)	None	15 (75.0%)	12 (60.0%)	12 (54.5%)	39 (62.9%)
	1 per day	3 (15.0%)	2 (10.0%)	2 (9.1%)	7 (11.3%)
	2 per day	0 (0.0%)	1 (5.0%)	0 (0.0%)	1 (1.6%)
	3+per day	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	2 (10.0%)	5 (25.0%)	8 (36.4%)	15 (24.2%)

[1]See Section 6.4 for details

Table 3. 25: (Visit4) - Summary statistics of EPIC-URINARY DOMAIN[1] subscales, by treatment arm (CHRONOS-B)

EPIC-URINARY DOMAIN subscales	Statistics	Focal + finasteride N=20	Focal + bicalutamide N=21	Focal alone N=22	Total N=63
Function	N	11	8	14	33
	Min	83.40	50.00	66.60	50.00
	Mean (SD)	95.78 (5.71)	86.9 (17.24)	90.97 (13.36)	91.59 (12.63)
	Median (IQR)	100 (93.4 to 100)	93.4 (79.2 to 100)	100 (78.4 to 100)	100 (88.4 to 100)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	9 (45%)	13 (61.9%)	8 (36.4%)	30 (47.6%)
Bother	N	10	8	14	32
	Min	57.14	29.17	46.43	29.17
	Mean (SD)	88.93 (12.54)	76.56 (26.68)	82.02 (16.85)	82.81 (18.65)
	Median (IQR)	91.07 (85.71 to 96.43)	89.88 (55.36 to 96.43)	91.07 (67.86 to 92.86)	91.07 (69.64 to 96.43)
	Max	100	100	100	100
	Ungradable – n (%)	1 (5%)	0 (0.0%)	0 (0.0%)	1 (1.6%)
	Missing from eCRF – n (%)	10 (50%)	13 (61.9%)	8 (36.4%)	31 (49.2%)
Incontinence	N	11	8	14	33
	Min	73	43.75	39.5	39.5
	Mean (SD)	91.89 (10.06)	87.53 (18.7)	89.16 (19.92)	89.67 (16.5)
	Median (IQR)	100 (85.5 to 100)	92.75 (85.5 to 100)	100 (91.75 to 100)	100 (85.5 to 100)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	9 (45%)	13 (61.9%)	8 (36.4%)	30 (47.6%)
Irritative/ Obstructive	N	10	8	14	32
	Min	75.00	41.67	42.86	41.67
	Mean (SD)	93.93 (7.72)	78.2 (25.32)	85.2 (15.08)	86.18 (17.14)
	Median (IQR)	94.64 (92.86 to 100)	91.96 (51.79 to 98.21)	92.86 (78.57 to 92.86)	92.86 (78.57 to 96.43)
	Max	100	100	100	100
	Ungradable – n (%)	1 (5%)	0 (0.0%)	0 (0.0%)	1 (1.6%)
	Missing from eCRF – n (%)	10 (50%)	13 (61.9%)	8 (36.4%)	31 (49.2%)
Urinary Summary	N	11	8	14	33
	Min	72.25	38.64	57.67	38.64
	Mean (SD)	92.14 (8.25)	81.02 (22.31)	85.83 (13.32)	86.77 (14.86)
	Median (IQR)	91.67 (88.92 to 97.92)	91.54 (65.29 to 97.92)	89.25 (79.17 to 95.83)	91.67 (79.92 to 97.92)
	Max	100	100	100	100
	Ungradable – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing from eCRF – n (%)	9 (45%)	13 (61.9%)	8 (36.4%)	30 (47.6%)
EPIC-Urinary (Q5, Pad usage) – n (%)	None	11 (55.0%)	7 (33.3%)	13 (59.1%)	31 (49.2%)
	1 per day	0 (0.0%)	1 (4.8%)	1 (4.5%)	2 (3.2%)
	2 per day	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3+per day	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	9 (45.0%)	13 (61.9%)	8 (36.4%)	30 (47.6%)

[1]See Section 6.4 for details

Figure 10:(visit1) - Histograms of EQ-5D-5L dimensions and levels in CHRONOS A for each treatment group

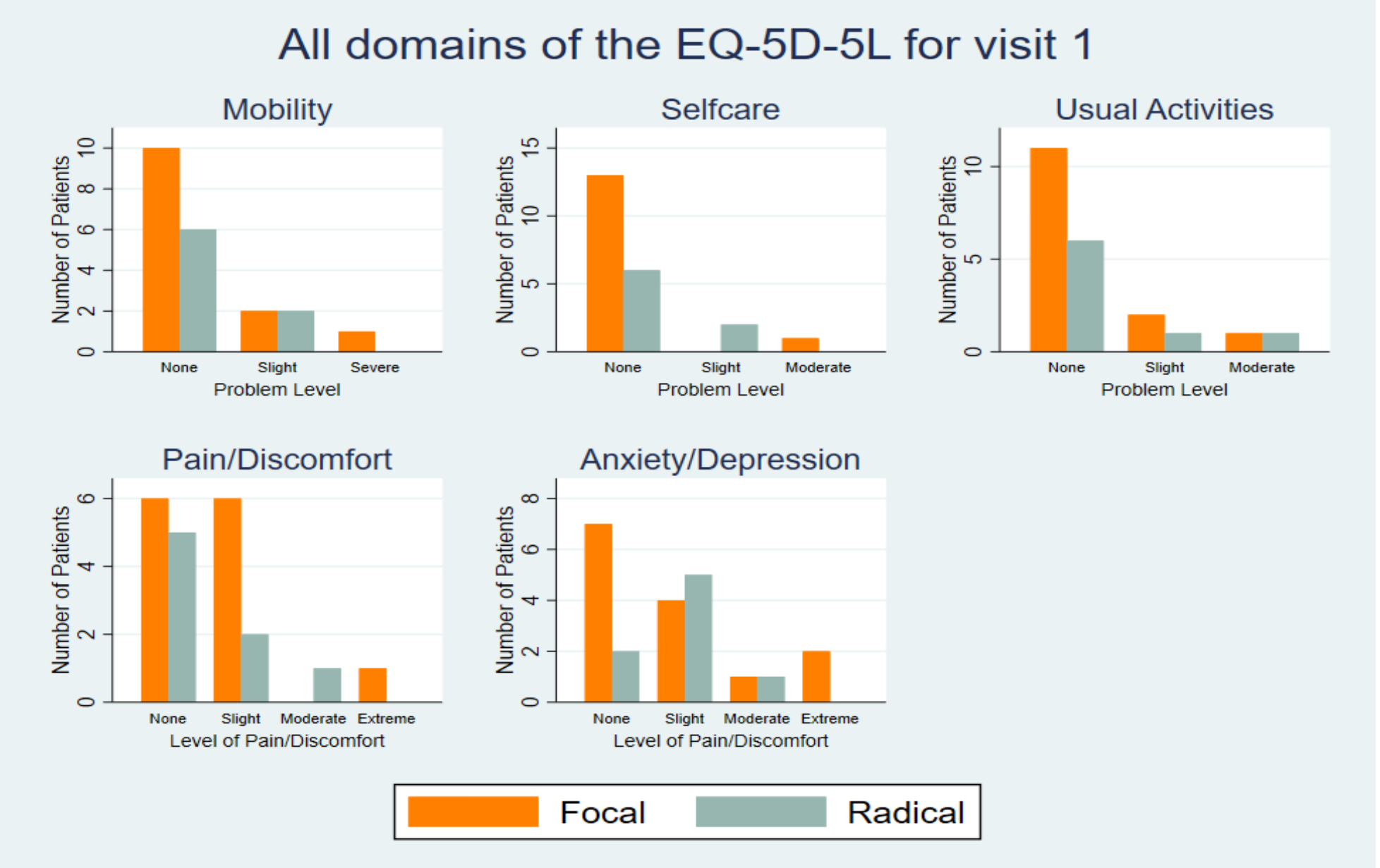


Figure 11:(visit3) - Histograms of EQ-5D-5L dimensions and levels in CHRONOS A for each treatment group

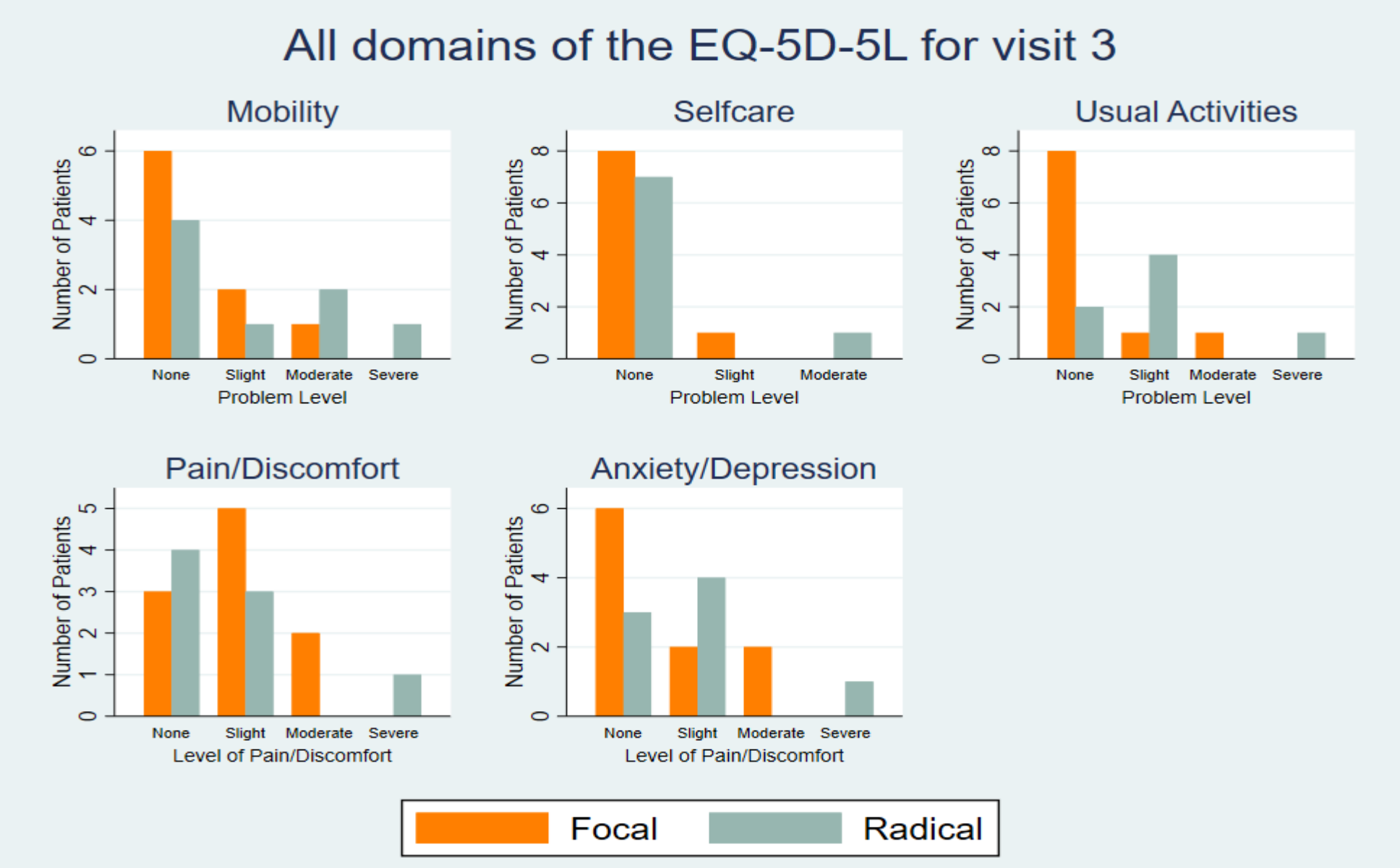


Figure 12:(visit1) - Histograms of EQ-5D-5L dimensions and levels in CHRONOS B for each treatment group

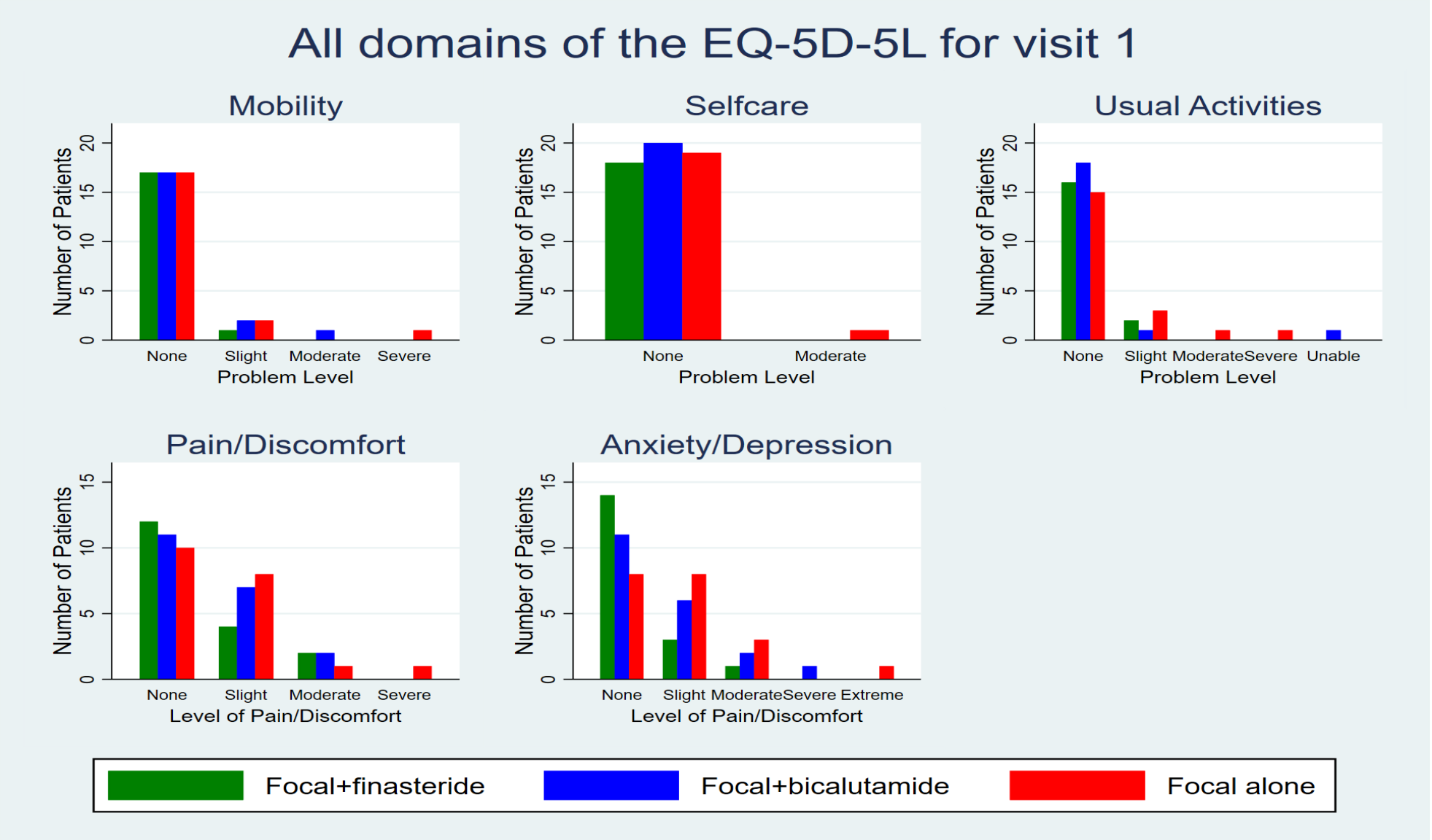


Figure 13:(visit3) - Histograms of EQ-5D-5L dimensions and levels in CHRONOS B for each treatment group

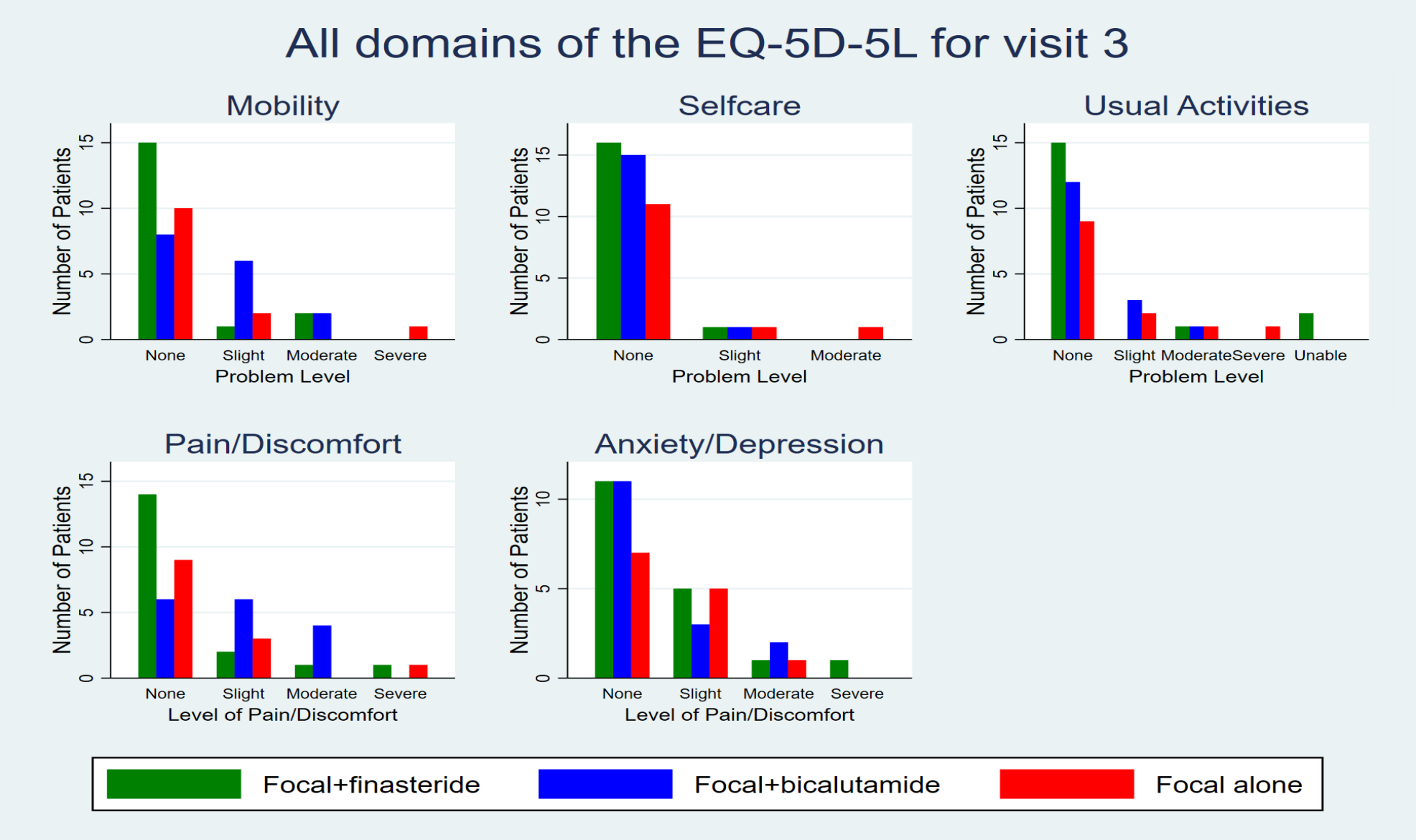


Figure 14:(visit4) - Histograms of EQ-5D-5L dimensions and levels in CHRONOS B for each treatment group

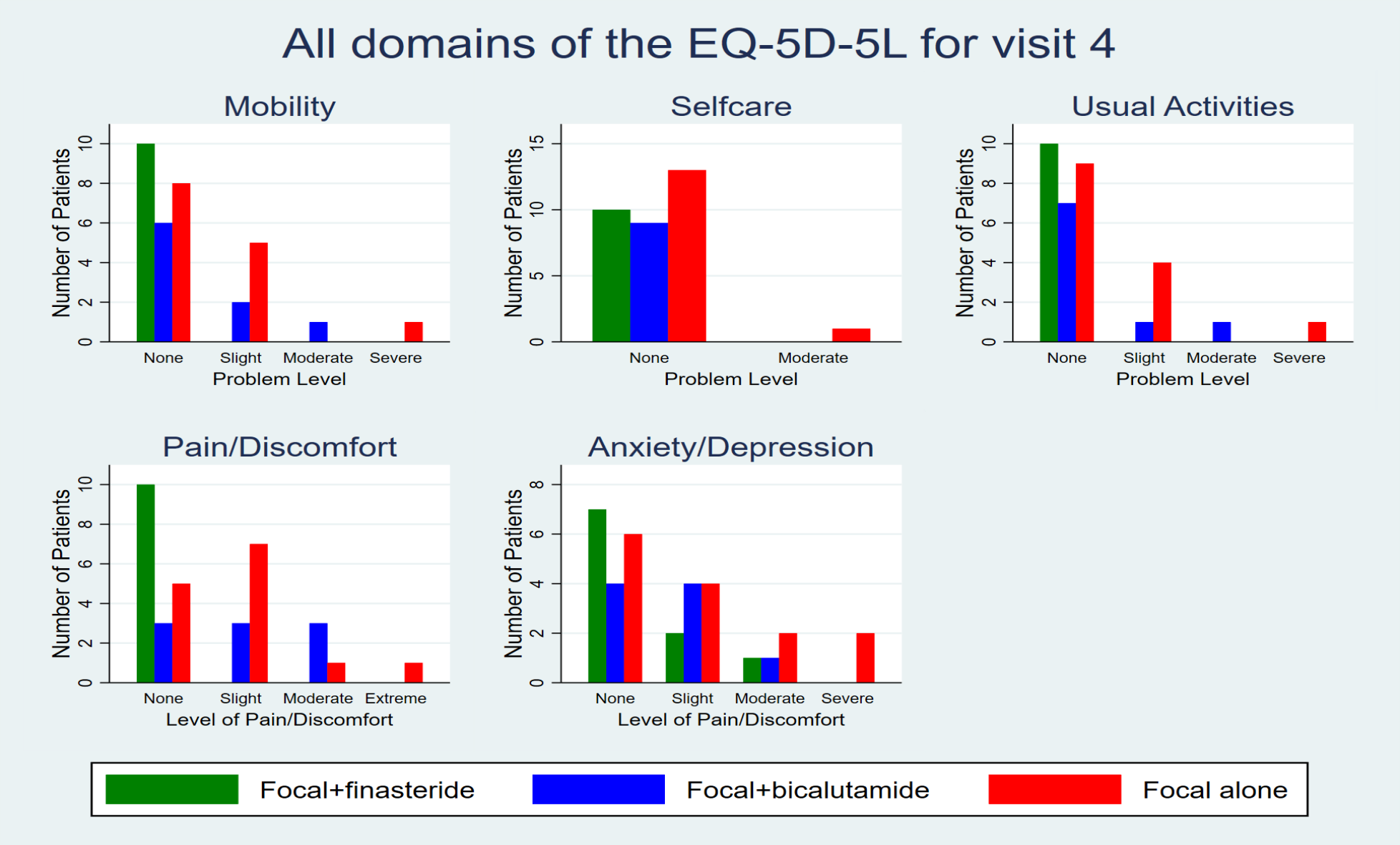


Figure 15: Graph to show change in mean EQ VAS scores (and corresponding 95% confidence intervals) from randomisation to 3 months for CHRONOS A

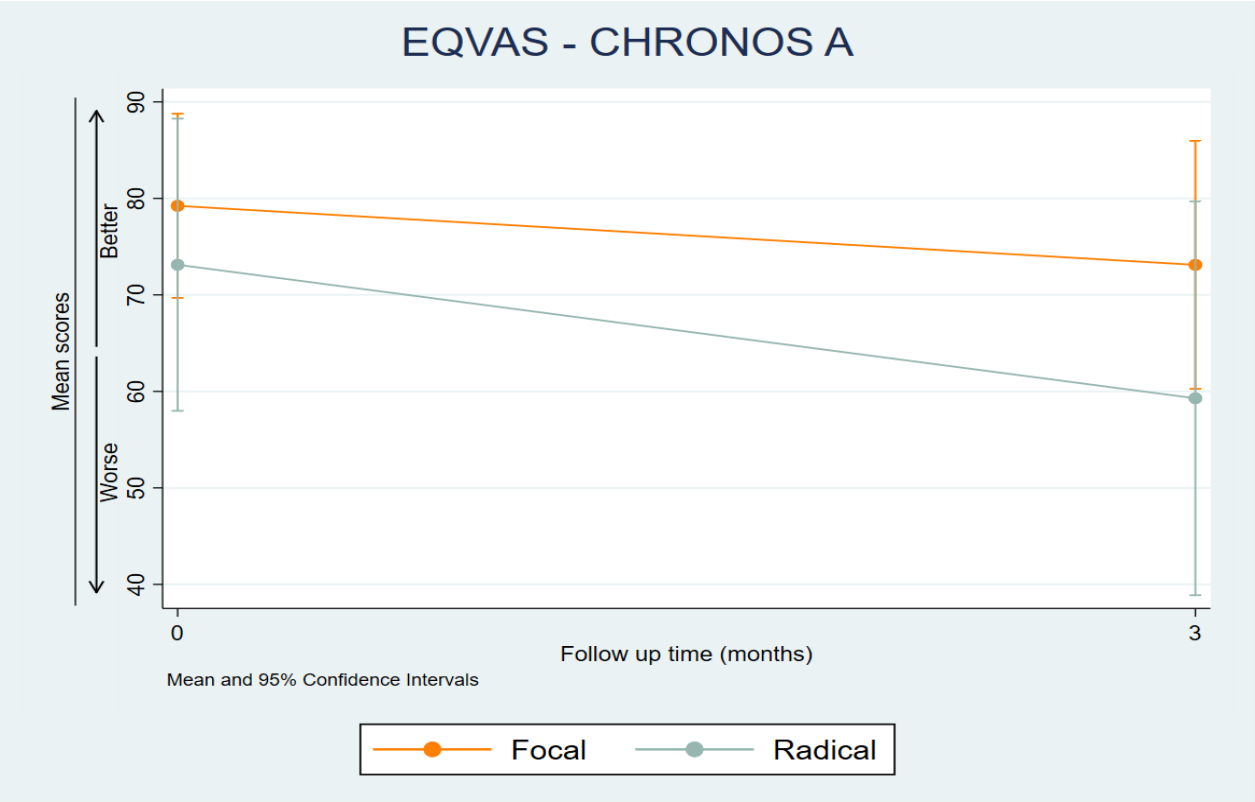


Figure 16: Graph to show change in mean EQ VAS scores (and corresponding 95% confidence intervals) from randomisation to 12 months for CHRONOS B

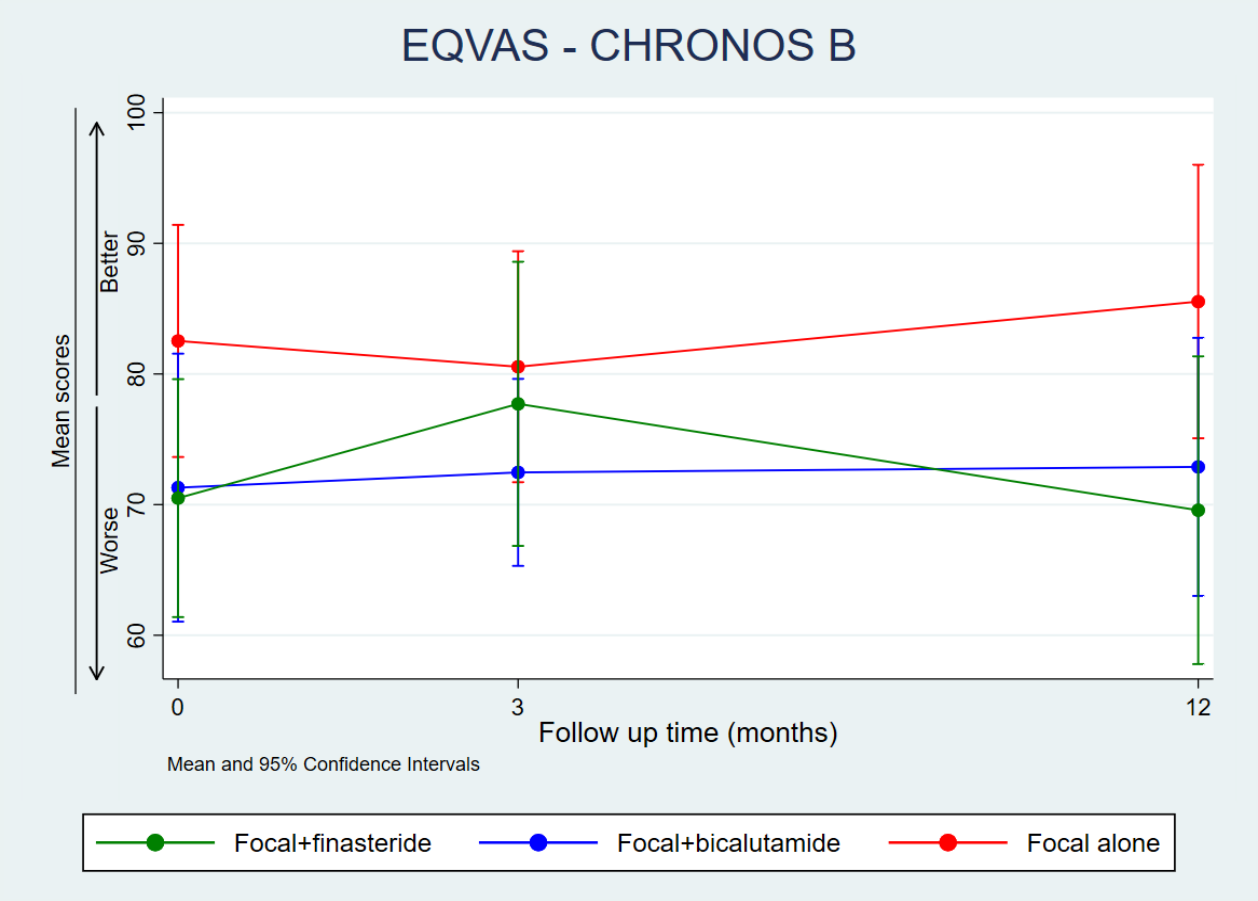


Figure 17: Graph to show change in mean for IIEF dimensions scores (and corresponding 95% confidence intervals) from randomisation to 3 months for CHRONOS A

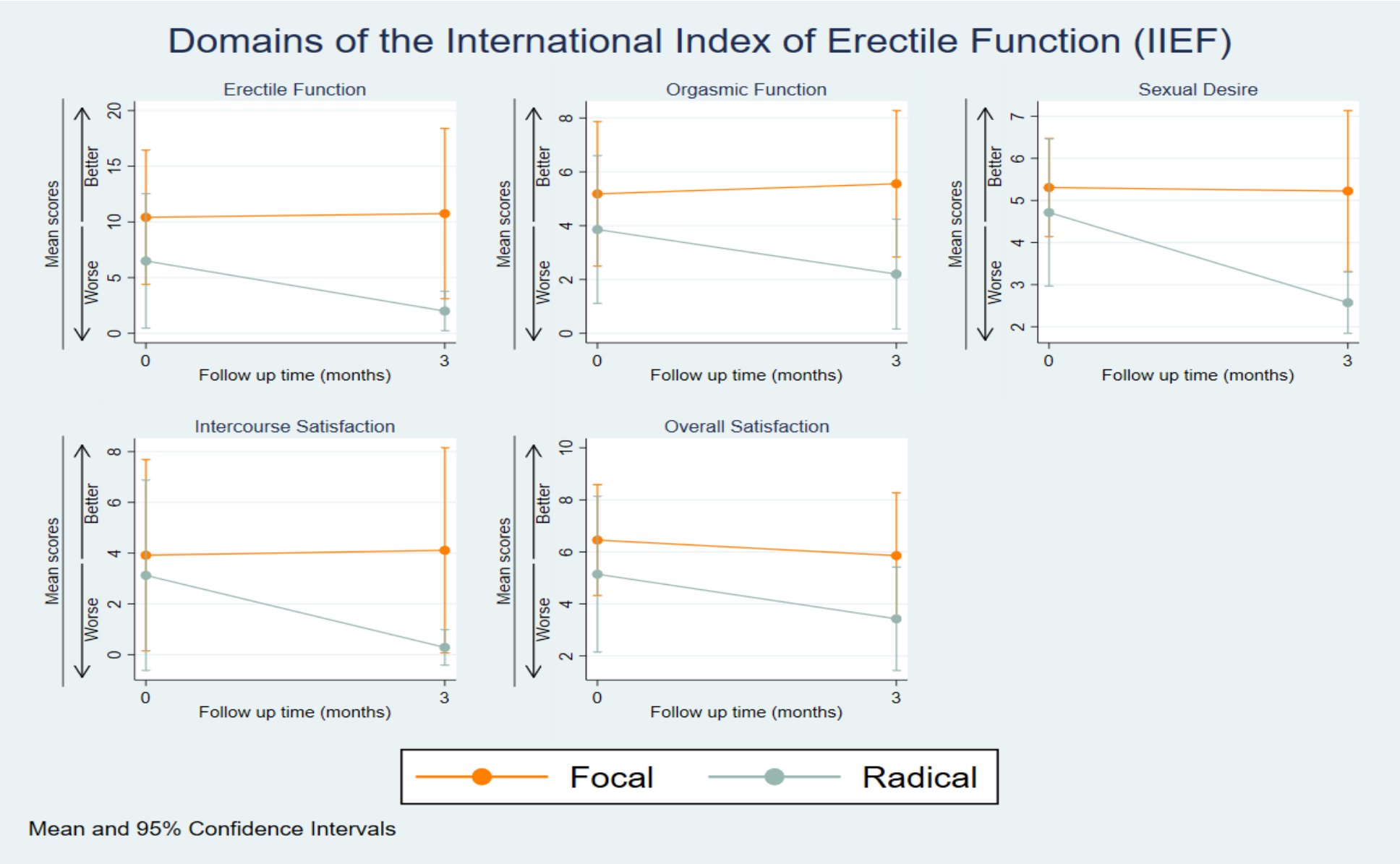


Figure 18: Graph to show change in mean for IIEF dimensions scores (and corresponding 95% confidence intervals) from randomisation to 12 months for CHRONOS B

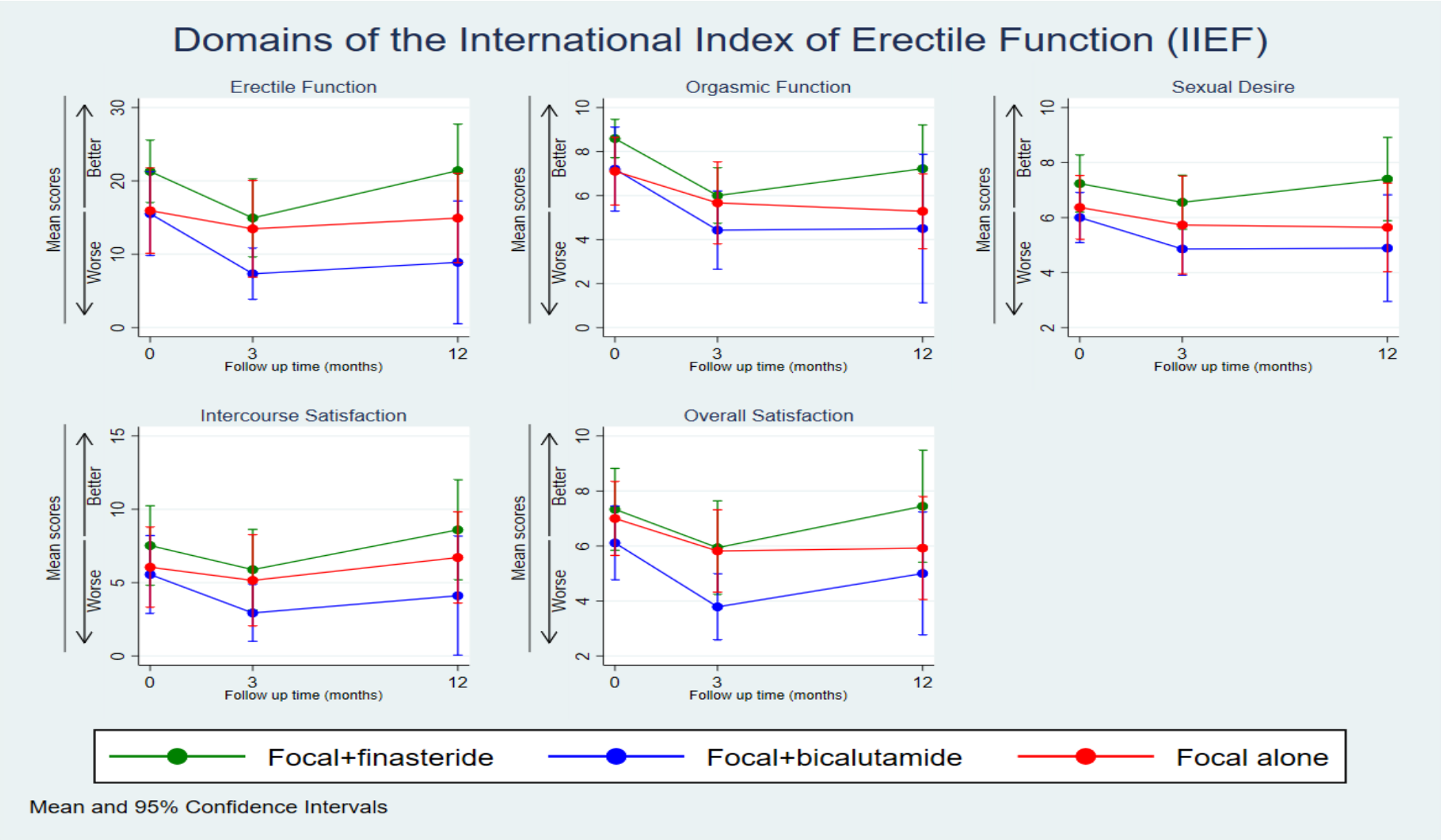


Figure 19: Graph to show change in mean for the five EPIC-26 dimensions scores (and corresponding 95% confidence intervals) from randomisation to 3 months for CHRONOS A

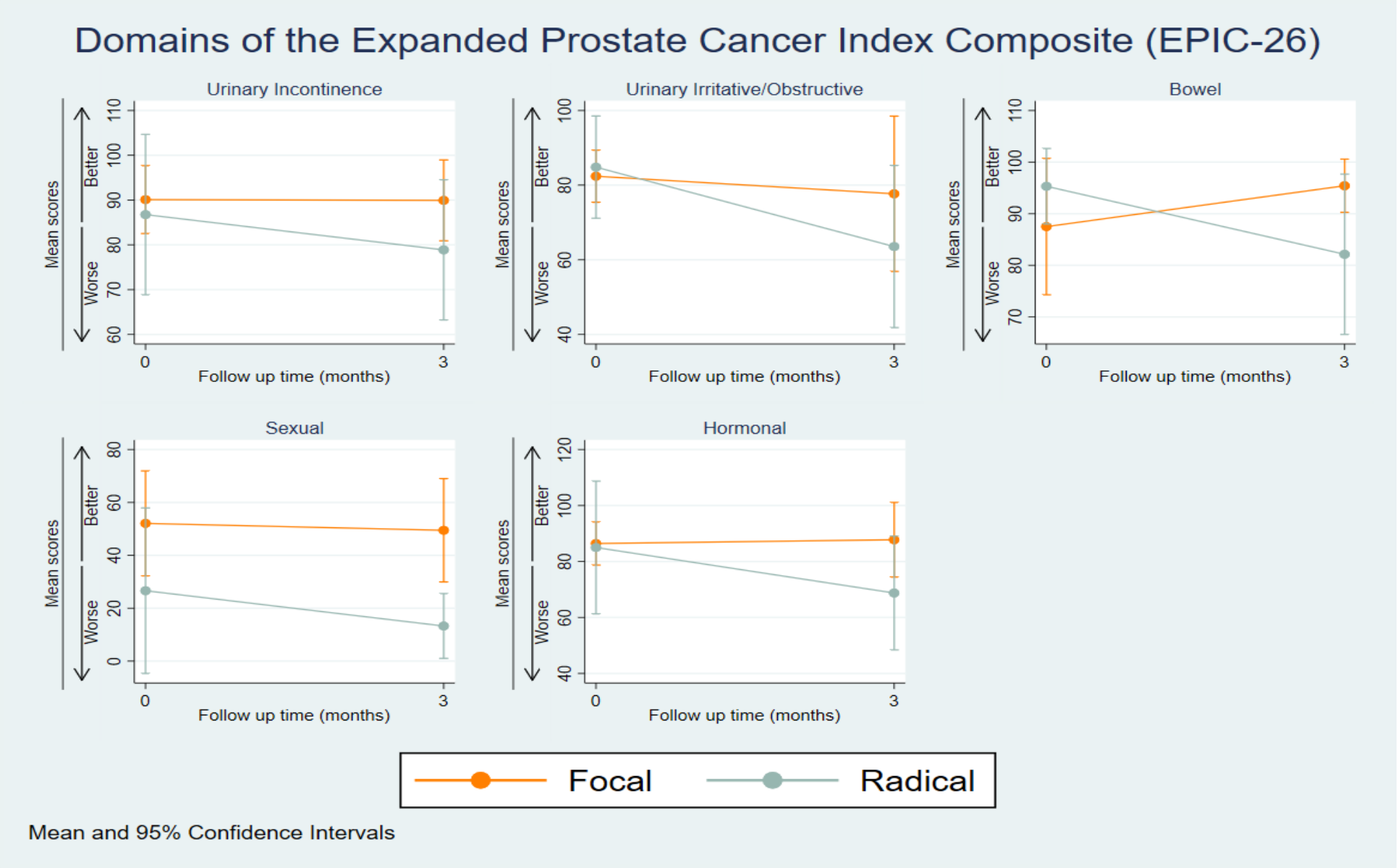


Figure 20: Graph to show change in mean for the five EPIC-26 dimensions scores (and corresponding 95% confidence intervals) from randomisation to 12 months for CHRONOS B

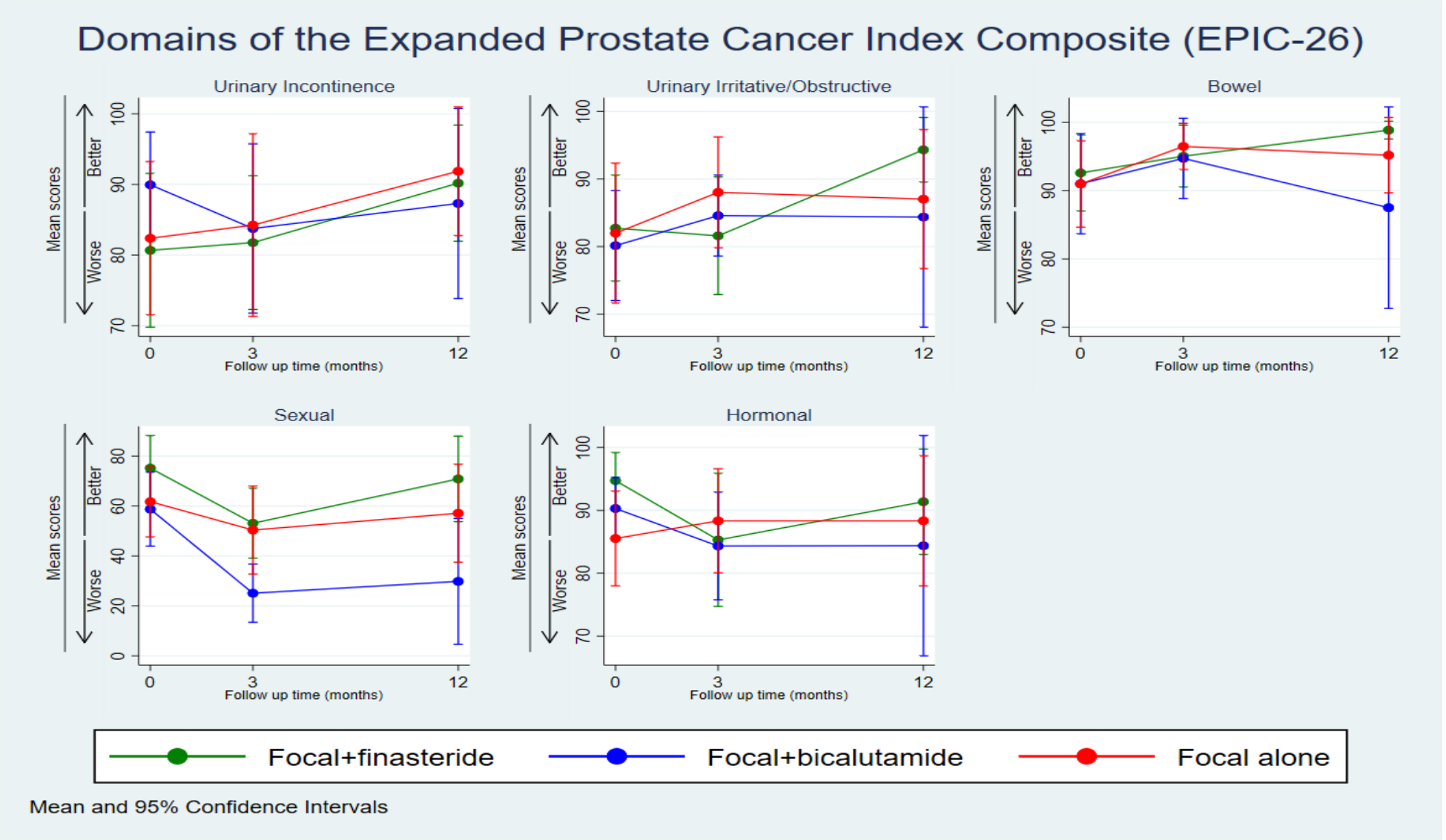


Figure 21: Graph to show change in mean for the five EPIC-URINARY DOMAIN subscales scores (and corresponding 95% confidence intervals) from randomisation to 3 months for CHRONOS A

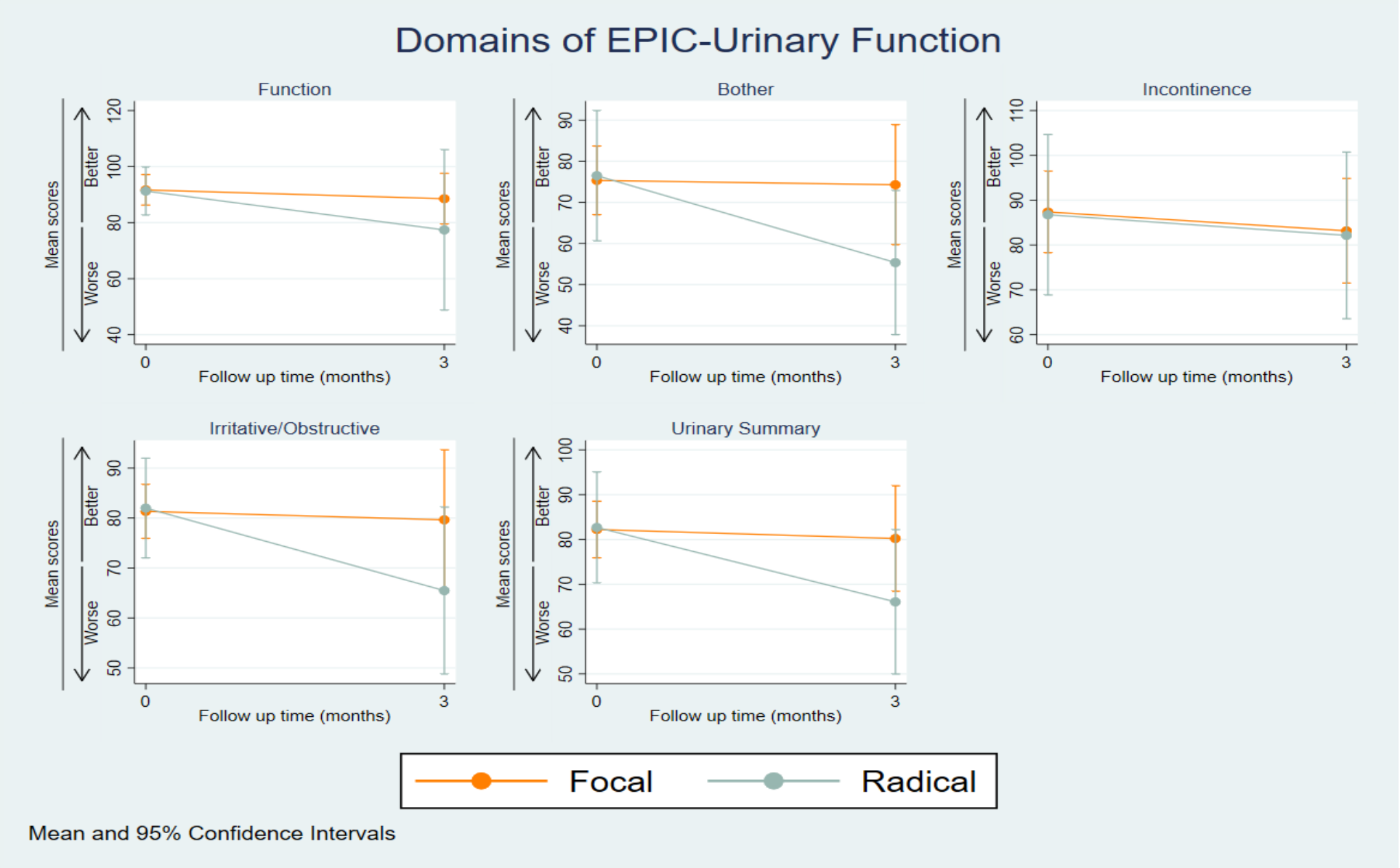


Figure 22: Graph to show change in mean for the five EPIC-URINARY DOMAIN subscales scores (and corresponding 95% confidence intervals) from randomisation to 12 months for CHRONOS B

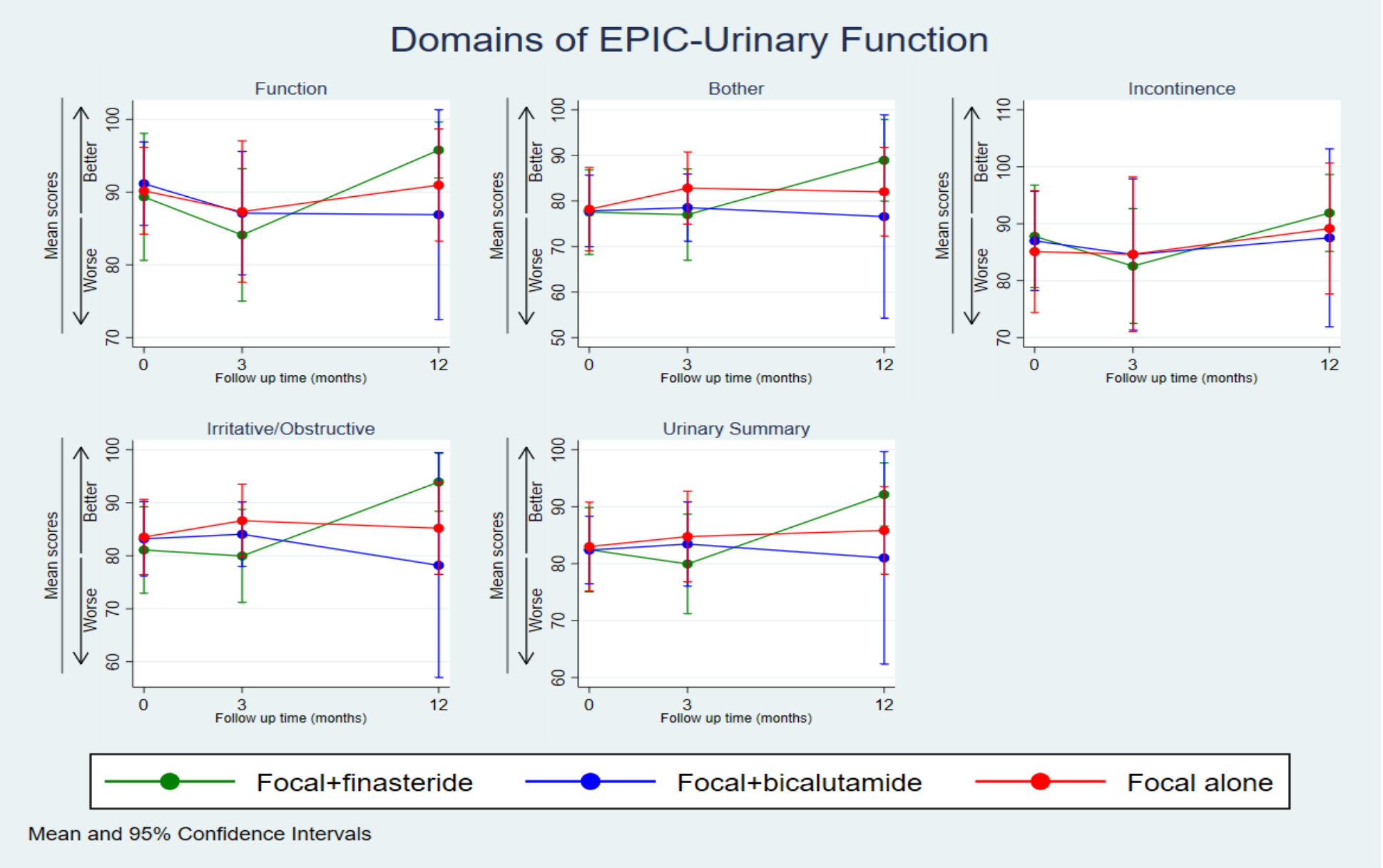


Figure 23: Histograms of Pad usage (Q5)- EPIC-Urinary by Visit for CHRONOS A

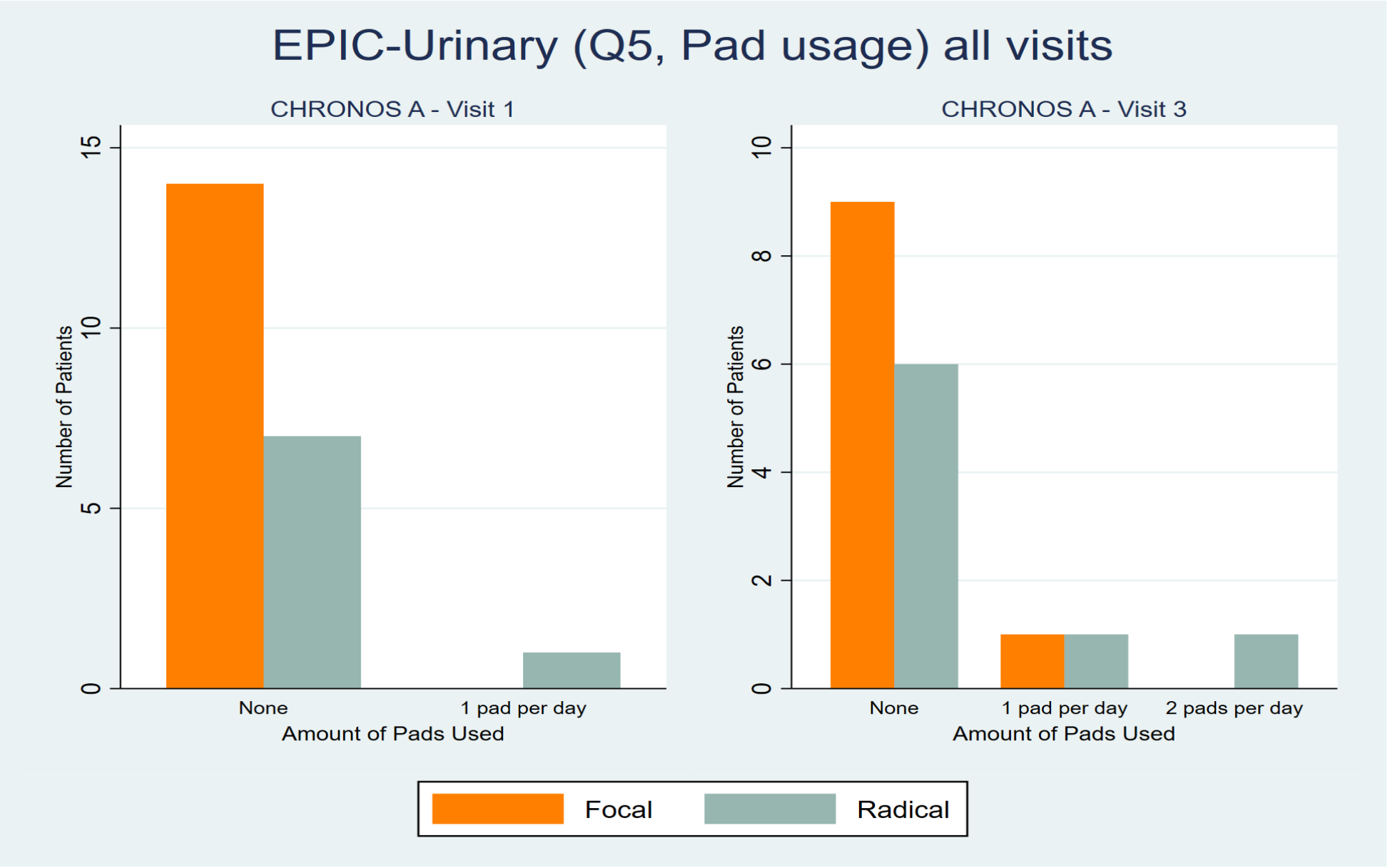
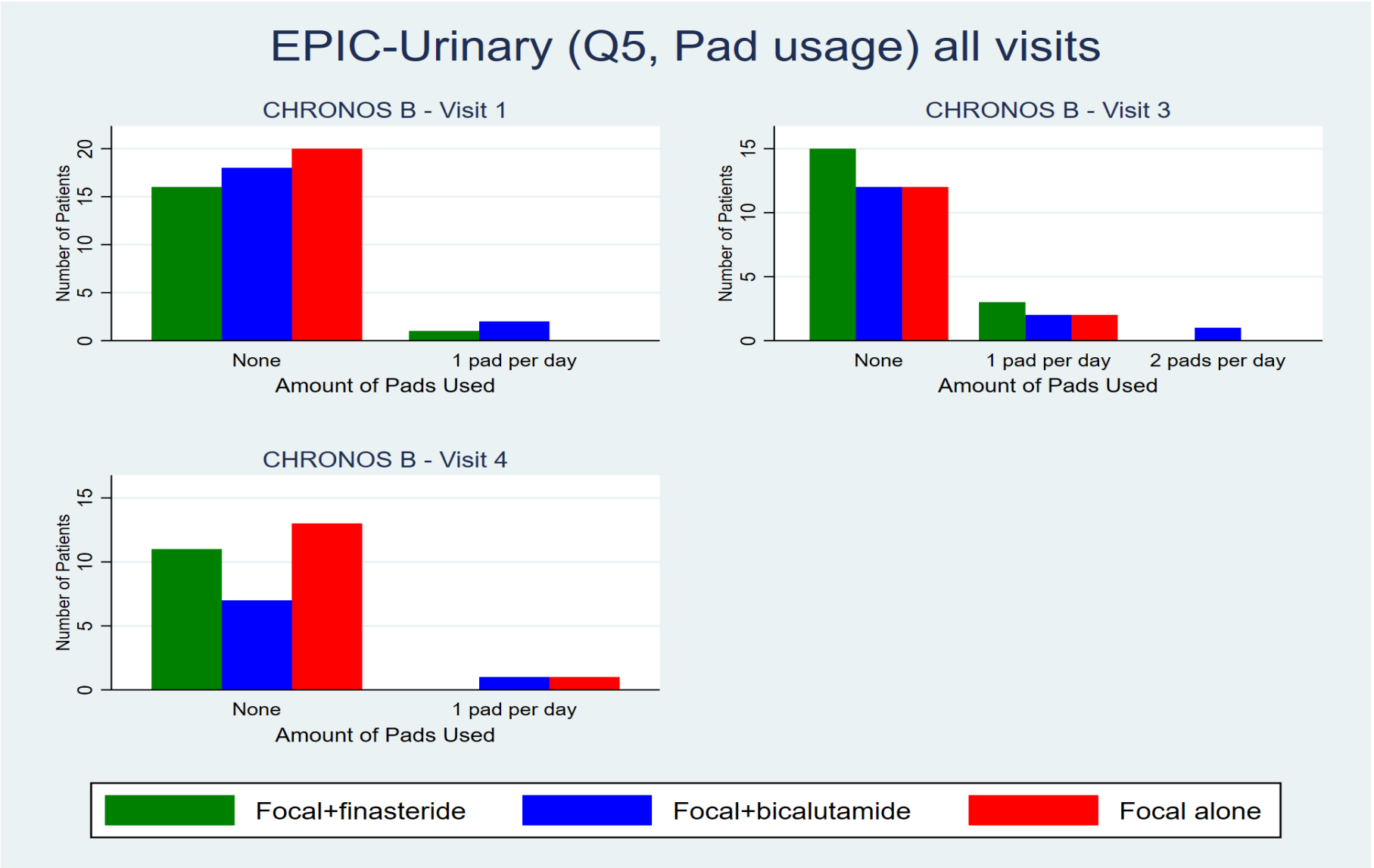


Figure 24: Histograms of Pad usage (Q5)- EPIC-Urinary by Visit for CHRONOS B



8.4.1. Protocol Deviations/Violations

Table 4. 1: Listing of Protocol Deviations and Violations for CHRONOS A

Patient ID	Treatment Group	Site[1]	Date Reported	Deviation (PD) or Violation (PV)	How Identified?	Description of PD/PV	Classification	Date of PD/PV	Response to PD/PV
CHR11-068	Focal	CHR11	06/01/2023	Protocol Deviation	By Coordinating centre	Visit 4 date is out of visit window schedule.	Study visit windows	27/06/2022	Visit assessment data uploaded two days after window when back in the office.
CHR2-047	Focal	CHR2	05/01/2021	Protocol Deviation	By site	abandoning HIFU	Other	05/01/2021	Offer whole gland radical therapy
CHR2-075	Focal	CHR2	12/09/2022	Protocol Deviation	By site	Participant did not undergo a 12 mth repeat bx as not deemed necessary as no suspicion on MRI to warrant invasive procedure	Sampling / laboratory measurements	07/09/2022	none
CHR2-079	Focal	CHR2	15/02/2022	Protocol Deviation	By Coordinating centre	This is in relation to visit 3.Patient had visit 3 days before study visit window	Study visit windows	10/11/2021	None
CHR2-088	Focal	CHR2	13/12/2021	Protocol Deviation	By site	Patient CHR2-088 did not have HIFU due to too high risk of ,perioperative death	Other	16/11/2021	HIFU-cancelled
CHR2-089	Focal	CHR2	08/11/2022	Protocol Deviation	By site	12mth Bx not done as not deemed necessary	Sampling / laboratory measurements	28/09/2022	none
CHR2-099	Focal	CHR2	14/12/2022	Protocol Deviation	By site	12 month Biopsy was not performed as not deemed necessary	Sampling / laboratory measurements	23/11/2022	None
CHR1-100	Radical	CHR1	24/01/2022	Protocol Deviation	By site	Patient did not undergo DCE sequences on MRI scan. Patient withdrew from study before repeat was performed	Variation in clinical management of participant	29/11/2021	Nil, patient withdrew
CHR11-072	Radical	CHR11	26/01/2022	Protocol Deviation	By site	opted out randomisation arm	Randomisation	29/04/2021	Patient wishes to have focal therapy. Their care transferred to CXH. Patient is happy to remain on the Chronos study.
CHR2-053	Radical	CHR2	11/01/2022	Protocol Deviation	By Coordinating centre	visit was outside the visit schedule window.in April the clinic was fully booked and unfortunately we were unable to see the patient. Deviation is in relation to visit 3.	Other	17/03/2021	not slot available in April 2021
CHR2-067	Radical	CHR2	04/01/2023	Protocol Deviation	By site	visit date is out of visit window schedule	Study visit windows	21/10/2022	not slot available in window schedule

[1]Site Mnemonic:

CHR1 - Charing Cross Hospital
CHR2 - University Hospital Southampton NHS Foundation Trust
CHR11 – West Middlesex University Hospital

Table 4. 2: Number of Protocol Deviations and Violations for CHRONOS A

Type of Deviation/Violation	Focal	Radical	Total
Inclusion/exclusion criteria	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study drug administration	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sampling/laboratory measurements	**3 (42.9%)**	0 (0.0%)	**3 (27.3%)**
Consent issue	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study visit windows	**2 (28.6%)**	**1 (25.0%)**	**3 (27.3%)**
NIMP administration	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study drug prescription	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dispensing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Accountability	0 (0.0%)	0 (0.0%)	0 (0.0%)
Compliance	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missed study visit	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study measurements/assessments[1]:	0 (0.0%)	0 (0.0%)	0 (0.0%)
Primary outcome measure	0 (0.0%)	0 (0.0%)	0 (0.0%)
Secondary outcome measure	0 (0.0%)	0 (0.0%)	0 (0.0%)
Safety outcome	0 (0.0%)	0 (0.0%)	0 (0.0%)
Device	0 (0.0%)	0 (0.0%)	0 (0.0%)
Equipment	0 (0.0%)	0 (0.0%)	0 (0.0%)
Prohibited medication/substance(s)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE/SAE reporting	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blinding/unblinding	0 (0.0%)	0 (0.0%)	0 (0.0%)
Randomisation[2]:	0 (0.0%)	**1 (25.0%)**	**1 (9.1%)**
Opted out randomisation arm	0 (0.0%)	**1 (100.0%)**	**1 (100.0%)**
(Reason for deviation)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Implementation of document prior to research approval	0 (0.0%)	0 (0.0%)	0 (0.0%)
Licence/certification/calibration/servicing (labs and equipment)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Delegation log/authorisation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dose interruptions/modifications not specified in protocol	0 (0.0%)	0 (0.0%)	0 (0.0%)
Variation in clinical management of participant	0 (0.0%)	**1 (25.0%)**	**1 (9.1%)**
Withdrawal issue	0 (0.0%)	0 (0.0%)	0 (0.0%)
Falsifying research or medical records	0 (0.0%)	0 (0.0%)	0 (0.0%)
Repeated protocol deviations (of same type)	0 (0.0%)	0 (0.0%)	0 (0.0%)
COVID-19 Related[3]:	0 (0.0%)	0 (0.0%)	0 (0.0%)
(Please specify)	0 (0.0%)	0 (0.0%)	0 (0.0%)
(Please specify)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other[4]:	**2 (28.6%)**	**1 (25.0%)**	**3 (27.3%)**
Visit was outside the visit schedule window	0 (0.0%)	**1 (100.0%)**	**1 (33.3%)**
HIFU not done	**1 (50.0%)**	0 (0.0%)	**1 (33.3%)**
Abandoning HIFU	**1 (50.0%)**	0 (0.0%)	**1 (33.3%)**
Total	**7 (63.6%)**	**4 (36.4%)**	**11 (100%)**

[1-4]Italicized types are subcategories of the main type of Deviation/Violation (bold types), and their percentages represent percentages of the total number of the type of Deviation/Violation in bold, not of all cases.

Table 4. 3: Listing of Protocol Deviations and Violations for CHRONOS B

Patient ID	Treatment Group	Site[1]	Date Reported	Deviation (PD) or Violation (PV)	How Identified?	Description of PD/PV	Classification	Date of PD/PV	Response to PD/PV
CHR1-002	Focal + bicalutamide	CHR1	28/10/2020	Protocol Deviation	By site	Patient did not return blister packs	NIMP administration	21/05/2020	Retraining - Explicitly ask patients to return blister packs on day of surgery
CHR1-002	Focal + bicalutamide	CHR1	21/01/2021	Protocol Deviation	By site	Visit 4 completed outside study window. Due on 21 May 2021, completed on 20 July 2021.	Study visit windows	20/07/2021	Future visits to be booked in line with Study schedule and patients standard of care
CHR1-002	Focal + bicalutamide	CHR1	29/04/2022	Protocol Deviation	By site	Visit 5 completed outside study window. Due on 19 Nov 2021, completed on 23 Feb 2022. Patient cancelled appointment on 13/12/2021 and DNA'ed appointment on 03/12/2021.	Study visit windows	23/02/2022	Future visits to be booked in line with Study schedule and patients standard of care
CHR1-008	Focal + bicalutamide	CHR1	28/10/2020	Protocol Deviation	By site	Patient did not return blister pack	NIMP administration	18/06/2020	Retraining - Explicitly ask patients to return blister packs on day of surgery
CHR1-008	Focal + bicalutamide	CHR1	23/12/2022	Protocol Deviation	By site	Visit 5 completed outside study window. Due on 17 December 2021, completed on 02 February 2022	Study visit windows	02/02/2022	Future visits to be booked in line with study schedule and patients standard of care
CHR1-017	Focal + bicalutamide	CHR1	28/10/2020	Protocol Deviation	By site	Patient did not return blister pack	NIMP administration	13/07/2020	Retraining - Explicitly ask patients to return blister packs on day of surgery
CHR1-017	Focal + bicalutamide	CHR1	21/01/2022	Protocol Deviation	By site	Visit 3 completed outside study window. Due on 05 October 2020, completed on 03 December 2020.	Study visit windows	03/12/2020	Future visits to be booked in line with Study schedule and patients standard of care.
CHR1-017	Focal + bicalutamide	CHR1	23/12/2022	Protocol Deviation	By site	Visit 6 completed outside study window. Due on 13 July 2022, completed on 06 April 2022	Study visit windows	06/04/2022	Future visits to be booked in line with study schedule and patients standard of care
CHR1-018	Focal + bicalutamide	CHR1	18/04/2020	Protocol Deviation	Other	remote consent was obtained, scan of consent seen and confirmed by clinical fellow. Patient then posted consent form to Charing cross hospital but delayed over 2 weeks. Required resending consent form	Consent issue	18/04/2020	Consent form reposted, both arrived and filed. Consent forms signed by investigator taking consent
CHR1-018	Focal + bicalutamide	CHR1	28/10/2020	Protocol Deviation	By site	Blister pack was not returned by participant	NIMP administration	13/07/2020	Retraining - Explicitly ask patients to return blister packs on day of surgery
CHR1-018	Focal + bicalutamide	CHR1	21/01/2022	Protocol Deviation	By site	Visit 3 completed outside study window. Due on 05 October 2020, completed on 02 December 2020.	Study visit windows	02/12/2020	Future visits to be booked in line with Study schedule and patients standard of care.
CHR1-034	Focal + bicalutamide	CHR1	27/10/2020	Protocol Deviation	By site	Due to COVID and subsequent remote working, a lag time on prescription	Study drug administration	10/07/2020	Minimum 12 weeks of IMP still given

						administration led to the IMP being given out of the 24 hour window.			
CHR1-034	Focal + bicalutamide	CHR1	28/10/2020	Protocol Deviation	By site	Participant did not return blister pack of IMP	NIMP administration	08/10/2020	Retraining - Explicitly ask patients to return blister packs on day of surgery
CHR1-034	Focal + bicalutamide	CHR1	23/12/2022	Protocol Deviation	By site	Visit 5 completed outside study window. Due on 08 April 2022, completed on 20 July 2022	Study visit windows	20/07/2022	Future visits to be booked in line with study schedule and patients standard of care
CHR1-037	Focal + bicalutamide	CHR1	27/10/2020	Protocol Deviation	By site	Due to COVID and subsequent remote working, a lag time on prescription administration led to the IMP being given out of the 24 hour window	Study drug administration	04/08/2020	Treatment adjusted to allow for delay
CHR1-037	Focal + bicalutamide	CHR1	16/12/2020	Protocol Deviation	By site	Patient did not return blister pack	Study drug administration	29/10/2020	Patients are reminded at consent to retain their blister packs and return them on day of surgery
CHR1-038	Focal + bicalutamide	CHR1	16/12/2020	Protocol Deviation	By site	Blister pack not returned	Study drug administration	07/12/2020	Already discussed, reminder to site sent out.
CHR1-038	Focal + bicalutamide	CHR1	05/12/2021	Protocol Deviation	By site	Visit 3 completed outside visit window. Due on 18 Feb 2021, completed on 24 Mar 2021	Study visit windows	24/11/2021	Further visits to be completed as per trial schedule and patient's standard of care visits.
CHR1-038	Focal + bicalutamide	CHR1	05/12/2021	Protocol Deviation	By site	Visit 4 completed outside study window. Due on 26 Nov 2021, completed on 20 Oct 2021	Study visit windows	20/10/2021	Future visits to be booked in line with Study schedule and patients standard of care.
CHR1-044	Focal + bicalutamide	CHR1	29/01/2021	Protocol Deviation	By site	Blister pack not returned by patient	Study drug administration	21/01/2021	Patient contacted to ensure he had stopped IMP, he had.
CHR1-057	Focal + bicalutamide	CHR1	27/08/2021	Protocol Deviation	By site	Patient did not return empty blister packs	NIMP administration	22/04/2021	Retraining - Explicitly ask patients to return blister packs on day of surgery
CHR1-057	Focal + bicalutamide	CHR1	23/12/2022	Protocol Deviation	By site	Visit 4 completed outside study window. Due on 22 April 2022, completed on 25 May 2022	Study visit windows	22/04/2022	Future visits to be booked in line with study schedule and patients standard of care
CHR11-064	Focal + bicalutamide	CHR11	19/02/2021	Protocol Deviation	By site	the delay in starting of bicalutamide	Dispensing	09/02/2021	CNS sent a letter to GP requesting dispensing
CHR2-005	Focal + bicalutamide	CHR2	28/05/2021	Protocol Deviation	By site	Biopsy not done	Other	19/05/2021	patient is not too keen on a biopsy.
CHR2-023	Focal + bicalutamide	CHR2	29/10/2020	Protocol Deviation	By Coordinating centre	patient did not receive IMP within the 24hr window.	Study drug prescription	06/05/2020	due to covid regulation, the prescription was sent by mail
CHR2-023	Focal + bicalutamide	CHR2	12/10/2021	Protocol Deviation	By site	Patient did not undergo 12mth bx as MRI showed no evidence of residual/recurrent disease	Missed study visit	08/09/2021	Deviation completed

CHR2-023	Focal + bicalutamide	CHR2	03/01/2023	Protocol Deviation	By site	visit date for visit 5 is out of windows schedule.	Study visit windows	29/04/2022	the patient did not come for the appointment, the next free appointment was 29/04/22
CHR2-025	Focal + bicalutamide	CHR2	17/01/2022	Protocol Deviation	By Coordinating centre	visit was outside the visit schedule window	Study visit windows	07/07/2021	not slot available in August
CHR2-025	Focal + bicalutamide	CHR2	04/01/2023	Protocol Deviation	By site	visit date is out of visit window schedule	Study visit windows	23/03/2022	not slot available in window schedule
CHR2-056	Focal + bicalutamide	CHR2	11/01/2022	Protocol Deviation	By Coordinating centre	outside the visit schedule window. The first available appointment with PI was unfortunately only in September. Deviation in relation to visit 3	Study visit windows	15/09/2021	not slot available in
CHR3-042	Focal + bicalutamide	CHR3	02/02/2021	Protocol Deviation	By Coordinating centre	Blister pack not returned	Other	25/01/2021	None
CHR3-043	Focal + bicalutamide	CHR3	02/02/2021	Protocol Deviation	By Coordinating centre	Blister pack not returned	Other	25/01/2021	None
CHR4-013	Focal + bicalutamide	CHR4	20/07/2020	Protocol Deviation	By site	Patient did not return the empty blister packs, but reports that he took all tablets.	Compliance	20/07/2020	Accepted he did not have the blister packs.
CHR4-013	Focal + bicalutamide	CHR4	06/01/2023	Protocol Deviation	By Coordinating centre	Visit 5 is out of visit window schedule. Patient had telephone FU 09/11/2021.	Study visit windows	19/05/2022	Patient had telephone FU on 09/11/2021, however these notes were not available at time of CRF completion. May 2022 notes were therefore updated.
CHR4-032	Focal + bicalutamide	CHR4	25/11/2020	Protocol Deviation	By site	Cardiac issue discovered pre-operatively - treatment put on hold until safe to proceed.	Variation in clinical management of participant	26/10/2020	prescribed more trial medication-waiting for cardiology review before proceeding. Underwent Cryo 20/5/2021 after Transcatheter Aortic Valve Implantation
CHR4-032	Focal + bicalutamide	CHR4	17/08/2021	Protocol Deviation	By site	Patient did not return IMP blister pack	Study drug administration	20/05/2021	Site reminded to ask patients to return blister packs
CHR1-001	Focal + finasteride	CHR1	28/10/2020	Protocol Deviation	By site	Patient did not return empty blister pack	NIMP administration	02/04/2020	Retraining - Explicitly ask patients to return blister packs on day of surgery
CHR1-001	Focal + finasteride	CHR1	21/01/2022	Protocol Deviation	By site	Visit 4 completed outside study window. Due on 02 April 2021, completed on 19 May 2021	Study visit windows	19/05/2021	Future visits to be booked in line with study schedule and patients standard of care
CHR1-001	Focal + finasteride	CHR1	21/01/2022	Protocol Deviation	By site	Visit 3 completed outside visit window. Due on 25 June 2020, completed on 19 August 2020	Study visit windows	19/08/2020	Future visits to be booked in line with Study schedule and patients standard of care.

CHR1-001	Focal + finasteride	CHR1	23/12/2022	Protocol Deviation	By site	Visit 6 completed outside study window. Due on 02 April 2022, completed on 22 June 2022.	Study visit windows	02/04/2022	Patient had TURP on 12 May, so appointment was booked for after this date. Future visits to be booked in line with study schedule and patients standard of care.
CHR1-001	Focal + finasteride	CHR1	23/12/2022	Protocol Deviation	By site	Visit 7 completed outside study window. Due on 02 October 2022, completed on 09 November 2022.	Study visit windows	02/10/2022	Future visits to be booked in line with study schedule and patients standard of care.
CHR1-004	Focal + finasteride	CHR1	28/10/2020	Protocol Deviation	By site	Patient did not return blister pack	NIMP administration	13/07/2020	Retraining - Explicitly ask patients to return blister packs on day of surgery
CHR1-004	Focal + finasteride	CHR1	21/01/2022	Protocol Deviation	By site	Visit 3 completed outside study window. Due on 05 October 2020, completed 27 January 2021.	Study visit windows	27/01/2021	Future visits to be booked in line with Study schedule and patients standard of care.
CHR1-004	Focal + finasteride	CHR1	23/12/2022	Protocol Deviation	By site	Visit 6 completed outside study window. Due on 13 July 2022, completed on 21 September 2022	Study visit windows	21/09/2022	Future visits to be booked in line with study schedule and patients standard of care
CHR1-004	Focal + finasteride	CHR1	23/12/2022	Protocol Deviation	By site	Visit 5 completed outside study window. Due on 11 January 2022, completed on 24 November 2021	Study visit windows	24/11/2021	Future visits to be booked in line with study schedule and patients standard of care
CHR1-004	Focal + finasteride	CHR1	23/12/2022	Protocol Deviation	By site	Visit 7 completed outside study window. Due on 12 January 2023, completed on 02 December 2022	Study visit windows	02/12/2022	Future visits to be booked in line with study schedule and patients standard of care
CHR10-061	Focal + finasteride	CHR10	12/01/2022	Protocol Deviation	By site	PROMS questionnaires completed outside visit window for Visit 3.	Study visit windows	06/06/2021	retrained via Trial Manager on telephone 12.01.22
CHR1-014	Focal + finasteride	CHR1	28/10/2020	Protocol Deviation	By site	Patient did not return blister pack	NIMP administration	25/06/2020	Retraining - Explicitly ask patients to return blister packs on day of surgery
CHR1-014	Focal + finasteride	CHR1	23/12/2022	Protocol Deviation	By site	Visit 6 completed outside study window. Due on 25 June 2022, completed on 18 May 2022	Study visit windows	18/05/2022	Future visits to be booked in line with study schedule and patients standard of care
CHR1-021	Focal + finasteride	CHR1	28/10/2020	Protocol Deviation	By site	Participant did not return IMP blister pack	NIMP administration	16/07/2020	Retraining - Explicitly ask patients to return blister packs on day of surgery
CHR1-027	Focal + finasteride	CHR1	16/12/2020	Protocol Deviation	By site	Blister pack not returned	Study drug administration	23/11/2020	Reminder sent to site to tell patients to bring their empty blister packs in on day of surgery
CHR1-027	Focal + finasteride	CHR1	15/09/2021	Protocol Deviation	By site	Patient DNAed the 3month follow up appointment. Appointment completed at 7 months.	Study visit windows	02/06/2021	Follow-up booked according to protocol. PSA taken and 1 year MRI booked
CHR1-027	Focal + finasteride	CHR1	01/12/2021	Protocol Deviation	By site	Visit 4 completed on 25/08/2021, 3 months ahead of schedule 1 year study visit date of 23/11/2021.	Study visit windows	25/08/2021	Visit completed in line with standard care plan for the patient

CHR1-027	Focal + finasteride	CHR1	24/01/2022	Protocol Deviation	By site	Study visit 3 fell out of window	Study visit windows	02/06/2021	Visit investigations organised.
CHR1-027	Focal + finasteride	CHR1	29/12/2022	Protocol Deviation	By site	Visit 5 completed outside study window. Due on 24 May 2022, completed on 23 Feb 2022	Study visit windows	23/02/2022	Future visits to be booked in line with study schedule and patients standard of care
CHR1-036	Focal + finasteride	CHR1	16/12/2020	Protocol Deviation	By site	Patient did not return blister pack	Study drug administration	22/10/2020	Site reminded to tell patients to return blister packs on day of surgery
CHR1-036	Focal + finasteride	CHR1	05/01/2022	Protocol Deviation	By site	Visit 5 completed outside study window. Due on 22 April 2022, completed on 05 January 2022	Study visit windows	05/01/2022	Future visits to be booked in line with study schedule and patients standard of care
CHR1-039	Focal + finasteride	CHR1	27/10/2020	Protocol Deviation	By site	Due to COVID and subsequent remote working, a lag time on prescription administration led to the IMP being given out of the 24 hour window	Study drug administration	27/08/2020	Amended day of surgery to ensure 12 weeks of IMP
CHR1-039	Focal + finasteride	CHR1	16/12/2020	Protocol Deviation	By site	Patient did not return their blister packs on day of surgery	Study drug administration	23/11/2020	Patients are reminded at consent to retain their blister packs and return them on day of surgery
CHR1-039	Focal + finasteride	CHR1	28/12/2022	Protocol Deviation	By site	Visit 5 completed outside study window. Due on 24 May 2022, completed on 05 Oct 2022	Study visit windows	05/10/2022	Future visits to be booked in line with Study schedule and patients standard of care.
CHR1-040	Focal + finasteride	CHR1	27/10/2020	Protocol Deviation	By site	Due to COVID19 pandemic and remote / distant administering of prescriptions there was a lag time from IMP was available	Study drug administration	27/08/2020	Date of surgery amended to ensure 12 weeks of IMP
CHR1-040	Focal + finasteride	CHR1	16/12/2020	Protocol Deviation	By site	Blister pack not returned by patient	Study drug administration	03/12/2020	Patients are reminded at consent to retain their blister packs and return them on day of surgery
CHR1-040	Focal + finasteride	CHR1	28/12/2022	Protocol Deviation	By site	Visit 5 completed outside study window. Due on 03 Jun 2022, completed on 10 Aug 2022	Study visit windows	10/08/2022	Future visits to be booked in line with Study schedule and patients standard of care.
CHR1-048	Focal + finasteride	CHR1	27/08/2021	Protocol Deviation	By site	Patient did not return empty blister pack	NIMP administration	25/02/2021	Retraining - Explicitly ask patients to return blister packs on day of surgery
CHR2-006	Focal + finasteride	CHR2	19/05/2020	Protocol Deviation	By site	incomplete treatment	Dose interruptions / modifications not specified in the protocol	19/05/2020	patient says he took one tablets every day. Tablets has been dispensed 12/02/20, HIFU was 19/05/20. The patient did not take 6 tablets
CHR2-010	Focal + finasteride	CHR2	20/08/2021	Protocol Deviation	By Coordinating centre	12MTH F/U BX NOT PERFORMED. Bx performed at 6mths due to rising PSA and suspicious PET scan results	Variation in clinical management of participant	03/12/2020	Deviation completed and study site informed

CHR2-010	Focal + finasteride	CHR2	03/01/2023	Protocol Deviation	By site	visit date is out of visit	Study visit windows	09/03/2022	the visit that was booked for January 2022 has been deleted and rebooked for March by the administrative team.
CHR2-026	Focal + finasteride	CHR2	11/01/2022	Protocol Deviation	By Coordinating centre	The first available appointment with the doctor was unfortunately only in November this deviation is in relation to visit 4	Study visit windows	03/11/2021	not slot available in August 2021
CHR2-028	Focal + finasteride	CHR2	22/10/2021	Protocol Deviation	By site	12 mth bx has not been undertaken, can not find any source data to explain reasoning why this has not been done	Sampling / laboratory measurements	22/09/2021	Deviation form completed
CHR2-045	Focal + finasteride	CHR2	16/10/2020	Protocol Deviation	By site	Cannot have MRI due to pacemaker	Inclusion/exclusion criteria	16/10/2020	The TM was contacted via email regarding this patients inability to have MRI due to pacemaker, the TM responded that the CI had been contacted and was happy for patient to be in trial.
CHR2-045	Focal + finasteride	CHR2	13/01/2021	Protocol Deviation	By site	delaying the procedure	AE/SAE reporting	24/12/2020	PATIENT WAS REFERED TO MYELOID CLINIC FOR INVESTIGATIONS Patient IMPs were delayed due to this referral
CHR2-045	Focal + finasteride	CHR2	23/03/2022	Protocol Deviation	By site	Unfortunately, he has a pacemaker and cannot have an MRI.	Other	23/03/2022	n/a
CHR2-052	Focal + finasteride	CHR2	04/02/2021	Protocol Deviation	By site	Patient was not sent study drug prescription within 24hrs due to Christmas/new year holidays and staff shortage issues	Study drug administration	06/01/2021	Patient was issued a prescription as soon as possible and commenced study drug
CHR2-059	Focal + finasteride	CHR2	06/05/2022	Protocol Deviation	By site	Patient underwent follow up bx before the 12mth appointment	Variation in clinical management of participant	22/10/2021	Reported to PI for explanation and advice
CHR2-060	Focal + finasteride	CHR2	31/08/2021	Protocol Deviation	By site	Participant completed 3/12 of Finasteride in May but did not have HIFU procedure until August	Study drug administration		Reported to Trial centre manager
CHR4-031	Focal + finasteride	CHR4	09/10/2020	Protocol Deviation	By site	Patient did not complete study drug course - stopped 23/09/2020	Dose interruptions / modifications not specified in the protocol	23/09/2020	PI and study centre aware
CHR4-031	Focal + finasteride	CHR4	17/01/2022	Protocol Deviation	By site	No 12 month biopsy performed	Study measurements /assessments	07/01/2021	As per study amendment, 12 month biopsies not required in MRI negative participants

CHR4-031	Focal + finasteride	CHR4	06/01/2023	Protocol Deviation	By Coordinating centre	Visit 6 date is out of window schedule. The date updated for visit 6 is the the closest available according to patient's EPR. The patient had T/FU on 01/11/2022.	Study visit windows	01/11/2022	The date updated for visit 6 is the closest available according to patient's EPR. The patient had telephone FU on 01/11/2022, therefore CRF was updated with this date.
CHR1-003	Focal alone	CHR1	21/01/2022	Protocol Deviation	By site	Visit 4 completed outside study window. Due on 02 April 2021, completed 21 July 2021.	Study visit windows	21/07/2021	Future visits to be booked in line with Study schedule and patients standard of care.
CHR1-003	Focal alone	CHR1	29/04/2022	Protocol Deviation	By site	Visit 5 completed outside study window. Due on 01 Oct 2021, completed on 09 Feb 2022.	Study visit windows	09/02/2022	Future visits to be booked in line with Study schedule and patients standard of care
CHR1-003	Focal alone	CHR1	23/12/2022	Protocol Deviation	By site	Visit 7 completed outside study window. Due on 02 October 2022, completed on 11 November 2022.	Study visit windows	02/10/2022	Future visits to be booked in line with study schedule and patients standard of care
CHR1-003	Focal alone	CHR1	23/12/2022	Protocol Deviation	By site	Visit 6 completed outside study window. Due on 02 April 2022, completed on 11 May 2022.	Study visit windows	02/04/2022	Future visits to be booked in line with study schedule and patients standard of care.
CHR1-007	Focal alone	CHR1	21/01/2022	Protocol Deviation	By site	Visit 4 completed outside study window. Due on 25 June 2021, completed on 11 August 2021.	Study visit windows	11/08/2021	Future visits to be booked in line with Study schedule and patients standard of care.
CHR1-007	Focal alone	CHR1	23/12/2022	Protocol Deviation	By site	Visit 6 completed outside study window. Due on 25 June 2022, completed on 13 April 2022.	Study visit windows	13/04/2022	Future visits to be booked in line with study schedule and patients standard of care
CHR1-007	Focal alone	CHR1	23/12/2022	Protocol Deviation	By site	Visit 5 completed outside study window. Due on 24 December 2021, completed on 13 October 2021	Study visit windows	13/10/2021	Future visits to be booked in line with study schedule and patients standard of care
CHR1-012	Focal alone	CHR1	22/09/2022	Protocol Deviation	By Coordinating centre	Missed Study Visit. Visit has not been booked by Study Team.	Missed study visit	29/05/2022	Escalated to PI
CHR1-016	Focal alone	CHR1	21/01/2022	Protocol Deviation	By site	Visit 3 completed outside study window. Due on 25 June 2020, completed on 26 August 2020.	Study visit windows	26/08/2020	Future visits to be booked in line with Study schedule and patients standard of care.
CHR1-016	Focal alone	CHR1	29/12/2022	Protocol Deviation	By site	Visit 6 was meant to occur on 02 Apr 2022. This visit was missed.	Study visit windows	02/04/2022	In future visits will be monitored more closely so they are not missed.
CHR1-019	Focal alone	CHR1	23/12/2022	Protocol Deviation	By site	Visit 6 completed outside study window. Due on 11 June 2022, completed on 20 October 2022	Study visit windows	11/06/2022	Future visits to be booked in line with study schedule and patients standard of care
CHR1-019	Focal alone	CHR1	23/12/2022	Protocol Deviation	By site	Visit 5 completed outside study window. Due on 10 December 2021, completed on 04 March 2022	Study visit windows	04/03/2022	Future visits to be booked in line with study schedule and patients standard of care
CHR1-030	Focal alone	CHR1	29/12/2022	Protocol Deviation	By site	Visit 6 completed outside study window. Due on 20 Aug 2022, completed on 24 June 2022	Study visit windows	24/06/2022	Future visits to be booked in line with study schedule and patients standard of care

CHR1-030	Focal alone	CHR1	29/12/2022	Protocol Deviation	By site	Visit 5 completed outside study window. Due on 18 Feb 2022, completed on 01 Dec 2021	Study visit windows	01/12/2021	Patient had a new de novo lesion so visit was conducted early.
CHR1-033	Focal alone	CHR1	23/12/2022	Protocol Deviation	By site	Visit 5 completed outside study window. Due on 25 March 2022, completed on 13 May 2022	Study visit windows	13/05/2022	Future visits to be booked in line with study schedule and patients standard of care
CHR1-035	Focal alone	CHR1	23/12/2022	Protocol Deviation	By site	Visit 5 completed outside study window. Due on 24 May 2022, completed on 12 January 2022	Study visit windows	12/01/2022	Future visits to be booked in line with study schedule and patients standard of care
CHR1-041	Focal alone	CHR1	28/12/2022	Protocol Deviation	By site	Visit 5 completed outside study window. Due on 15 July 2022, completed on 05 Oct 2022	Study visit windows	05/10/2022	Future visits to be booked in line with Study schedule and patients standard of care.
CHR2-049	Focal alone	CHR2	09/11/2021	Protocol Deviation	By site	Patient did not undergo 12mth Bx as was not deemed necessary and patient not keen to have one performed	Sampling / laboratory measurements	27/10/2021	Deviation completed
CHR2-049	Focal alone	CHR2	11/01/2022	Protocol Deviation	By Coordinating centre	patient anticipated departure from the UK in November. Deviation is in relation to visit 4	Study visit windows	27/10/2021	patient nit in UK in January 2022
CHR2-054	Focal alone	CHR2	27/07/2022	Protocol Deviation	By site	not PSA, visit 5	Other	27/07/2022	not PSA, visit 5. Patient out of Southampton.
CHR2-055	Focal alone	CHR2	29/03/2021	Protocol Deviation	By site	The patient ate a meal on the day HIFU	Other	25/02/2021	Deviation completed and study site informed
CHR2-055	Focal alone	CHR2	11/01/2022	Protocol Deviation	By Coordinating centre	Visit was outside the visit schedule window. The patient had a booked appointment number 3 in May because he was due to have HIFU in February, unfortunately the patient had a meal before the surgery and had to be moved to another day. Unfortunately, the administration refused to postpone the visit from May to June/July as there were no vacancies during the holiday season.	Study visit windows	26/05/2021	not slot available
CHR2-058	Focal alone	CHR2	04/01/2023	Protocol Deviation	By site	visit 4 is out of visit window schedule	Study visit windows	05/01/2022	not slot available in window schedule
CHR4-015	Focal alone	CHR4	06/11/2021	Protocol Deviation	By site	Patient admitted with a pulmonary embolus. Therefore biopsy postponed until anti coagulants discontinued	Sampling / laboratory measurements	06/11/2021	
CHR4-015	Focal alone	CHR4	17/01/2022	Protocol Deviation	By site	No 12 month biopsy performed	Study measurements /assessments	03/07/2021	No biopsy required in MRI negative men as per file note
CHR4-029	Focal alone	CHR4	06/01/2023	Protocol Deviation	By Coordinating centre	Visit 6 is out of visit window schedule. The patient was placed on self-supported management pathway. The patient's closest visit date after visit 5 is 08 Aug 2022, therefore this date was updated on the CRF as visit 6 date.	Study visit windows	08/08/2022	The patient was placed on self-supported management pathway. The closest visit date after visit 5 is Aug 2022, therefore this date was

									updated on the CRF as visit 6 date.
CHR4-046	Focal alone	CHR4	17/01/2022	Protocol Deviation	By site	Study visit fell outside of window	Study visit windows	15/07/2021	Site to prioritise as much a feasible to arrange follow-up within window

[1]Site Mnemonic:

CHR1 - Charing Cross Hospital
CHR2 - University Hospital Southampton NHS Foundation Trust
CHR3 - Sunderland Royal Hospital
CHR4 - Ashford and St. Peter's Hospitals (ASPH) NHS Foundation Trust
CHR10 – Kingston Hospital NHS Foundation Trust
CHR11 – West Middlesex University Hospital

Table 4. 4: Number of Protocol Deviations and Violations for CHRONOS B

Type of Deviation/Violation	Focal + finasteride	Focal + bicalutamide	Focal alone	Total
Inclusion/exclusion criteria	**1 (2.4%)**	0 (0.0%)	0 (0.0%)	**1 (1.0%)**
Study drug administration	**6 (14.3%)**	**4 (11.1%)**	0 (0.0%)	**10 (9.5%)**
Sampling/laboratory measurements	**1 (2.4%)**	0 (0.0%)	**2 (7.4%)**	**3 (2.9%)**
Consent issue	0 (0.0%)	**1 (2.8%)**	0 (0.0%)	**1 (1.0%)**
Study visit windows	**20 (47.6%)**	**15 (41.7%)**	**21 (77.8%)**	**56 (53.3%)**
NIMP administration	**5 (11.9%)**	**6 (16.7%)**	0 (0.0%)	**11 (10.5%)**
Study drug prescription	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dispensing	0 (0.0%)	**1 (2.8%)**	0 (0.0%)	**1 (1.0%)**
Accountability	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Compliance	0 (0.0%)	**1 (2.8%)**	0 (0.0%)	**1 (1.0%)**
Missed study visit	0 (0.0%)	**1 (2.8%)**	**1 (3.7%)**	**2 (1.9%)**
Study measurements/assessments[1]:	**1 (2.4%)**	0 (0.0%)	**1 (3.7%)**	**2 (1.9%)**
Primary outcome measure	**1 (100.0%)**	0 (0.0%)	**1 (100.0%)**	**2 (100.0%)**
Secondary outcome measure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Safety outcome	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Device	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Equipment	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Prohibited medication/substance(s)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE/SAE reporting	**1 (2.4%)**	0 (0.0%)	0 (0.0%)	**1 (1.0%)**
Blinding/unblinding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Randomisation[2]:	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
(Reason for deviation)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
(Reason for deviation)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Implementation of document prior to research approval	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Licence/certification/calibration/servicing (labs and equipment)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Delegation log/authorisation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dose interruptions/modifications not specified in protocol	**2 (4.8%)**	0 (0.0%)	0 (0.0%)	**2 (1.9%)**
Variation in clinical management of participant	**2 (4.8%)**	**1 (2.8%)**	0 (0.0%)	**3 (2.9%)**
Withdrawal issue	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Falsifying research or medical records	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Repeated protocol deviations (of same type)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
COVID-19 Related[3]:	**2 (4.8%)**	**3 (8.3%)**	**0 (0.0%)**	**5 (4.8%)**
A lag time on prescription administration led to the IMP being given out of the 24 hour window	**2 (100.0%)**	**3 (100.0%)**	0 (0.0%)	**5 (100.0%)**
Other[4]:	**1 (2.4%)**	**3 (8.3%)**	**2 (7.4%)**	**6 (5.7%)**
Blister pack not returned	0 (0.0%)	**2 (66.7%)**	0 (0.0%)	**2 (33.3%)**
Rebook HIFU	0 (0.0%)	0 (0.0%)	**1 (50.0%)**	**1 (16.7%)**
Biopsy is not done in visit 4	0 (0.0%)	**1 (33.3%)**	0 (0.0%)	**1 (16.7%)**
No 12 months MRI	**1 (100.0%)**	0 (0.0%)	0 (0.0%)	**1 (16.7%)**
Not PSA, visit 5	0 (0.0%)	0 (0.0%)	**1 (50.0%)**	**1 (16.7%)**
Total	**42 (40%)**	**36 (34.3%)**	**27 (25.7%)**	**105 (100.0%)**

[1-4]Italicized types are subcategories of the main type of Deviation/Violation (bold types), and their percentages represent percentages of the total number of the type of Deviation/Violation in bold, not of all cases.

9. Impact of the Covid-19 Pandemic

9.1. Analysis Populations

On 05/03/2020, Covid-19 was added to Public Health England's list of notifiable diseases in England and Wales (5).

10. Tables to Present

10.1.1. Baseline Characteristics

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

This table is not presented as patients were recruited and randomised on/after COVID-19 pandemic period.

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

This table is not presented as the results are the same as **Table 1.1** as patients were recruited and randomised on/after COVID-19 pandemic period.

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

Variable	Statistics	Focal + finasteride	Focal + bicalutamide	Focal Alone	Total
Age	N	4	4	5	13
	Mean (SD)	65.25 (3.30)	68.75 (5.50)	61.60 (7.80)	64.92 (6.33)
	Median (IQR)	65.00 (62.50-68.00)	67.50 (64.50-73.00)	57.00 (57.00-69.00)	65.00 (62.00-69.00)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity – n (%)	N	4	4	5	13
	White	4 (100.0%)	4 (100.0%)	3 (60.0%)	11 (84.6%)
	Mixed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Black	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (7.7%)
	Other	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (7.7%)
	Not Reported	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IMD Decile – n (%)	N	4	4	5	13
	1	1 (25.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	4	1 (25.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	5	1 (25.0%)	1 (25.0%)	2 (40.0%)	4 (30.8%)
	6	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (7.7%)
	7	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (7.7%)
	8	1 (25.0%)	1 (25.0%)	0 (0.0%)	2 (15.4%)
	9	0 (0.0%)	0 (0.0%)	2 (40.0%)	2 (15.4%)
	10	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (7.7%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Digital Rectal Examination – n (%)	N	4	4	5	13
	Yes:	1 (25.0%)	0 (0.0%)	1 (20.0%)	2 (15.4%)
	Normal findings[1]	1 (25.0%)	0 (0.0%)	1 (20.0%)	2 (15.4%)
	Abnormal findings[1]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	3 (75.0%)	4 (100.0%)	4 (80.0%)	11 (84.6%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Current medications – n (%)	N	4	4	5	13
	Yes	3 (75.0%)	3 (75.0%)	2 (40.0%)	8 (61.5%)
	No	1 (25.0%)	1 (25.0%)	3 (60.0%)	5 (38.5%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5 alpha-reductase inhibitor[2] – n (%)	N	4	4	5	13
	Yes over (or equal to) 6 months ago	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Yes within 6 months	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	4 (100.0%)	4 (100.0%)	5 (100.0%)	13 (100.0%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stratification Factors					
Tumour grade (n (%))	Gleason 3+3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Gleason 3+4	3 (75.0%)	3 (75.0%)	4 (80.0%)	10 (76.9%)
	Gleason 4+3	1 (25.0%)	1 (25.0%)	1 (20.0%)	3 (23.1%)
Local stage (n (%))	Clinical T2/Radiological stage <T3a	4 (100.0%)	4 (100.0%)	4 (80.0%)	12 (92.3%)
	Radiological T3a	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (7.7%)

*Patients were recruited during/after the Covid-19 pandemic if they were recruited to CHRONOS-B after 05/03/2020 (see Section 9.1)
[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 5. 4: Baseline characteristics, by treatment arm, for patients recruited to the trial during/after* the Covid-19 pandemic (CHRONOS-B)

Variable	Statistics	Focal + finasteride	Focal + bicalutamide	Focal alone	Total
Age	N	17	17	17	51
	Mean (SD)	65.82 (7.46)	66.00 (7.98)	65.41 (6.76)	65.75 (7.27)
	Median (IQR)	68.00 (64.00-69.00)	65.00 (60.00-72.00)	65.00 (62.00-71.00)	66.00 (60.00-71.00)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity – n (%)	N	17	17	17	51
	White	11 (64.7%)	13 (76.5%)	11 (64.7%)	35 (68.6%)
	Mixed	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (2.0%)
	Asian	0 (0.0%)	1 (5.9%)	0 (0.0%)	1 (2.0%)
	Black	1 (5.9%)	1 (5.9%)	0 (0.0%)	2 (3.9%)
	Other	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (2.0%)
	Not Reported	5 (29.4%)	2 (11.8%)	4 (23.5%)	11 (21.6%)
IMD Decile – n (%)	N	17	17	17	51
	1	0 (0.0%)	2 (11.8%)	0 (0.0%)	2 (3.9%)
	2	0 (0.0%)	0 (0.0%)	2 (11.8%)	2 (3.9%)
	3	1 (5.9%)	0 (0.0%)	1 (5.9%)	2 (3.9%)
	4	5 (29.4%)	3 (17.6%)	4 (23.5%)	12 (23.5%)
	5	3 (17.6%)	2 (11.8%)	2 (11.8%)	7 (13.7%)
	6	0 (0.0%)	1 (5.9%)	2 (11.8%)	3 (5.9%)
	7	3 (17.6%)	1 (5.9%)	1 (5.9%)	5 (9.8%)
	8	2 (11.8%)	3 (17.6%)	2 (11.8%)	7 (13.7%)
	9	2 (11.8%)	2 (11.8%)	2 (11.8%)	6 (11.8%)
	10	1 (5.9%)	3 (17.6%)	1 (5.9%)	5 (9.8%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Digital Rectal Examination – n (%)	N	17	17	17	51
	Yes:	6 (35.3%)	8 (47.1%)	6 (35.3%)	20 (39.2%)
	Normal findings[1]	2 (11.8%)	6 (35.3%)	3 (17.6%)	11 (21.6%)
	Abnormal findings[1]	4 (23.5%)	2 (11.8%)	3 (17.6%)	9 (17.6%)
		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	11 (64.7%)	9 (52.9%)	11 (64.7%)	31 (60.8%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Current medications – n (%)	N	17	17	17	51
	Yes	9 (52.9%)	12 (70.6%)	11 (64.7%)	32 (62.7%)
	No	8 (47.1%)	5 (29.4%)	6 (35.3%)	19 (37.3%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5 alpha-reductase inhibitor – n (%)	N	17	17	17	51
	Yes over (or equal to) 6 months ago	0 (0.0%)	1 (5.9%)	0 (0.0%)	1 (2.0%)
	Yes within 6 months	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No	17 (100.0%)	16 (94.1%)	17 (100.0%)	50 (98.0%)
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stratification Factors					
Tumour grade (n (%))	Gleason 3+3	0 (0.0%)	2 (11.8%)	2 (11.8%)	4 (7.8%)
	Gleason 3+4	14 (82.4%)	13 (76.5%)	12 (70.6%)	39 (76.5%)
	Gleason 4+3	3 (17.6%)	2 (11.8%)	3 (17.6%)	8 (15.7%)
Local stage (n (%))	Clinical T2/Radiological stage <T3a	14 (82.4%)	15 (88.2%)	16 (94.1%)	45 (88.2%)
	Radiological T3a	3 (17.6%)	2 (11.8%)	1 (5.9%)	6 (11.8%)

*Patients were recruited during/after the Covid-19 pandemic if they were recruited to CHRONOS-B after 05/03/2020 (see Section 9.1)
[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

10.1.2. 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)

	Centre	Number of patients		Period of recruitment[2] (months)	Mean number of patients per month[3]	
		Recruited	Randomised		Recruited	Randomised
CHRONOS-A	Charing Cross Hospital	-	-	-	-	-
	University Hospital Southampton NHS Foundation Trust	-	-	-	-	-
	Sunderland Royal Hospital	-	-	-	-	-
	Ashford & St Peter's Hospitals (ASPH) NHS Foundation Trust	-	-	-	-	-
	Royal Marsden Hospital NHS Foundation Trust	-	-	-	-	-
	Hampshire Hospital NHS Foundation Trust	-	-	-	-	-
	Kingston Hospital NHS Foundation Trust	-	-	-	-	-
	West Middlesex University Hospital	-	-	-	-	-
	The Newcastle Upon Tyne Hospitals NHS Foundation Trust	-	-	-	-	-
	King's College Hospital NHS Foundation Trust	-	-	-	-	-
	Total					
CHRONOS-B	Charing Cross Hospital	7	7	3	2.33	2.33
	University Hospital Southampton NHS Foundation Trust	5	5	2	2.50	2.50
	Sunderland Royal Hospital	0	0	0	0.00	0.00
	Ashford & St Peter's Hospitals (ASPH) NHS Foundation Trust	1	1	2	0.50	0.50
	Royal Marsden Hospital NHS Foundation Trust	0	0	0	0.00	0.00
	Kingston Hospital NHS Foundation Trust	0	0	0	0.00	0.00
	West Middlesex University Hospital	0	0	0	0.00	0.00
	Total	**13**	**13**			

[1]Patients were recruited before the Covid-19 pandemic if they were recruited to the trial before 05/03/2020 (see Section 9.1)
[2]Period of recruitment in months was calculated using the date that the sites were open for recruitment till the date that the recruitment was closed (30/11/2021) for CHRONOS A and up to 28/02/2021 for CHRONOS B minus the pause period (only for site 3) due to the COVID-19 pandemic.
[3]Mean number of patients per month was obtained by dividing the number of patients per site by the time in months for the recruited and randomised patients.

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)

	Centre	Number of patients		Period of recruitment[2] (months)	Mean number of patients per month[3]	
		Recruited	Randomised		Recruited	Randomised
CHRONOS-A	Charing Cross Hospital	4	4	24	0.17	0.17
	University Hospital Southampton NHS Foundation Trust	19	19	14	1.36	1.36
	Sunderland Royal Hospital	4	4	17	0.24	0.24
	Ashford & St Peter's Hospitals (ASPH) NHS Foundation Trust	0	0	23	0.00	0.00
	Royal Marsden Hospital NHS Foundation Trust	2	2	11	0.18	0.18
	Hampshire Hospital NHS Foundation Trust	1	1	6	0.17	0.17
	Kingston Hospital NHS Foundation Trust	0	0	12	0.00	0.00
	West Middlesex University Hospital	5	5	12	0.42	0.42
	The Newcastle Upon Tyne Hospitals NHS Foundation Trust	1	1	9	0.11	0.11
	King's College Hospital NHS Foundation Trust	0	0	6	0.00	0.00
	Total	**36**	**36**			
CHRONOS-B	Charing Cross Hospital	25	25	12	2.08	2.08
	University Hospital Southampton NHS Foundation Trust	17	17	12	1.42	1.42
	Sunderland Royal Hospital	2	2	8	0.25	0.25
	Ashford & St Peter's Hospitals (ASPH) NHS Foundation Trust	5	5	12	0.42	0.42
	Royal Marsden Hospital NHS Foundation Trust	0	0	4	0.00	0.00
	Kingston Hospital NHS Foundation Trust	1	1	3	0.33	0.33
	West Middlesex University Hospital	1	1	2	0.50	0.50
	Total	**51**	**51**			

*The mean number of patients recruited and randomised per month per centre for CHRONOS A shows the same results of Table 2.2

[1]Patients were recruited during/after the Covid-19 pandemic if they were recruited to the trial after 05/03/2020 (see Section 9.1)

[2]Period of recruitment in months was calculated using the date that the sites were open for recruitment till the date that the recruitment was closed (30/11/2021) for CHRONOS A and up to 28/02/2021 for CHRONOS B minus the pause period (only for site 3) due to the COVID-19 pandemic.

[3]Mean number of patients per month was obtained by dividing the number of patients per site by the time in months for the recruited and randomised patients.

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)

	Recruitment Rate	Randomisation Rate
CHRONOS-A	-	-
95% CI	-	-
CHRONOS-B	43.3% (13/30)	100.0% (13/13)
95% CI	25.5% to 62.6%	75.3% to 1*

[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 9.1)

(*) one-sided, 97.5% confidence interval

10.1.3. Figures to Present (COVID-19)

- **Graph displaying recruitment rate over time (CHRONOS-A and CHRONOS-B), for patients recruited to the trial before the Covid-19 pandemic**

Since the calculation of the recruitment rate by month needs information on number of patients approached by month and this information was only collected by site, these graphs were omitted.

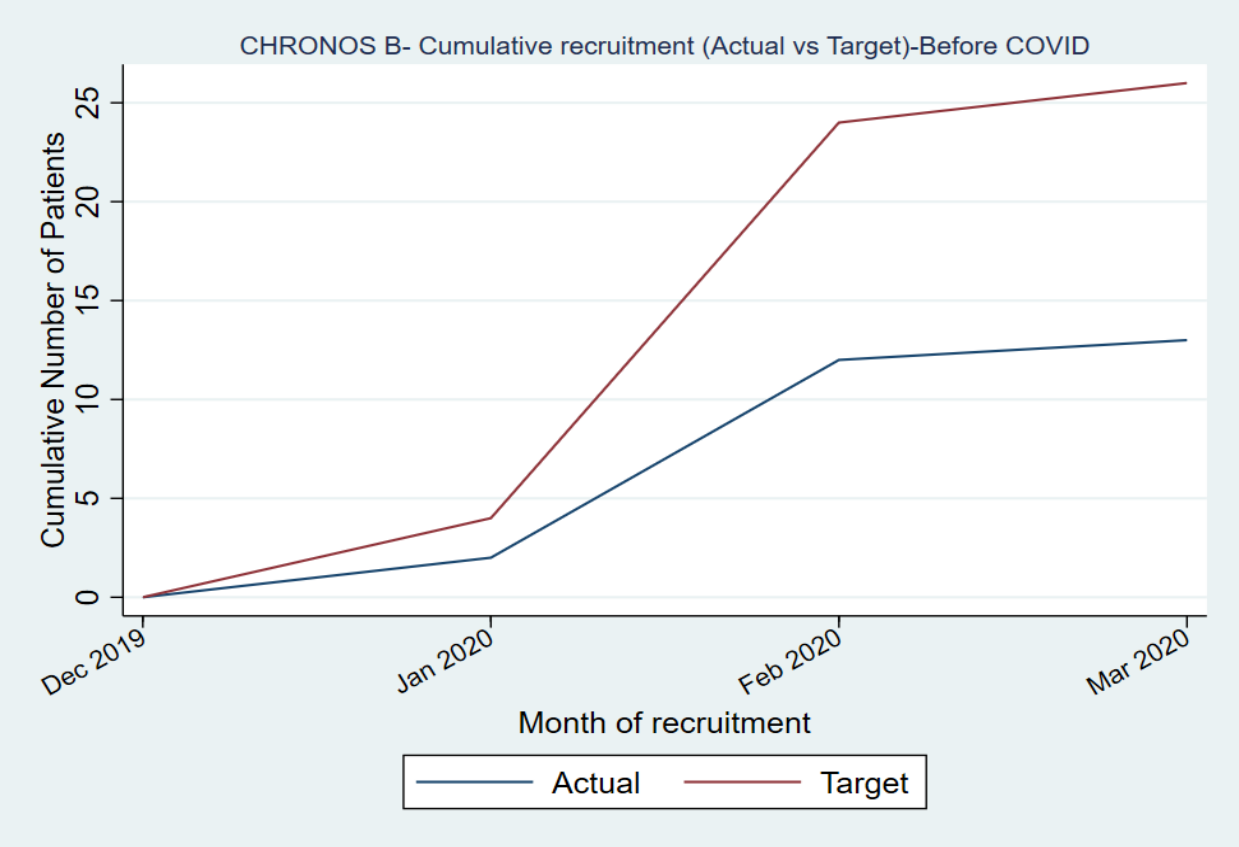
- **Graph displaying recruitment rate over time (CHRONOS-A and CHRONOS-B), for patients recruited to the trial during/after the Covid-19 pandemic**

Since the calculation of the recruitment rate by month needs information on number of patients approached by month and this information was only collected by site, these graphs were omitted.

- **Graph displaying the cumulative number of patients recruited over time (actual vs target) (CHRONOS-A) for patients recruited to the trial before the Covid-19 pandemic**

Since all patients were recruited during/after the Covid-19 pandemic, there is not data, and this graph was omitted.

Figure 25: Graph displaying the cumulative number of patients recruited over time (actual vs target) (CHRONOS-B) for patients recruited to the trial before[1] the Covid-19 pandemic

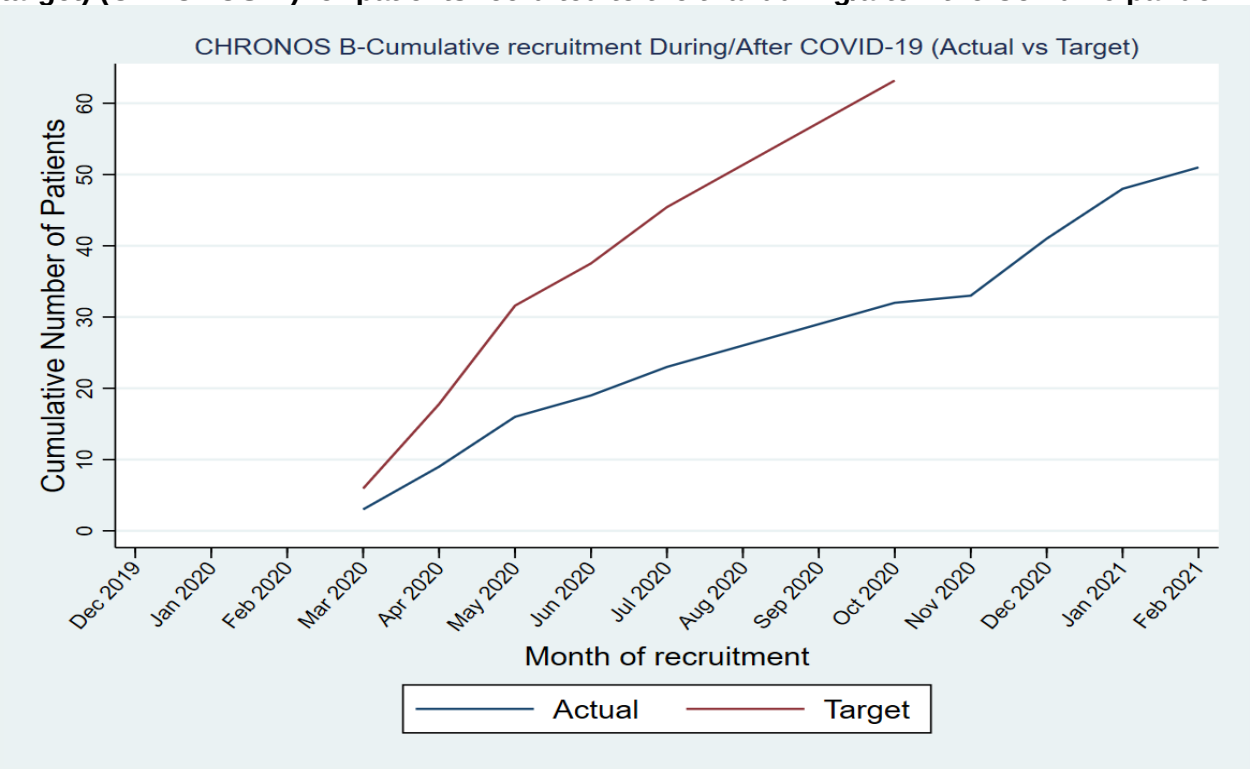


[1]Patients were recruited before the Covid-19 pandemic if they were recruited to the trial before 05/03/2020 (see Section 9.1)

- **Graph displaying the cumulative number of patients recruited over time (actual vs target) (CHRONOS-A) for patients recruited to the trial during/after the Covid-19 pandemic**

This graph was omited as **Figure 2** displays the same information, since all the patients were recruited during/after the Covid-19 pandemic.

Figure 26: Graph displaying the cumulative number of patients recruited over time (actual vs target) (CHRONOS-B) for patients recruited to the trial during/after[1] the Covid-19 pandemic

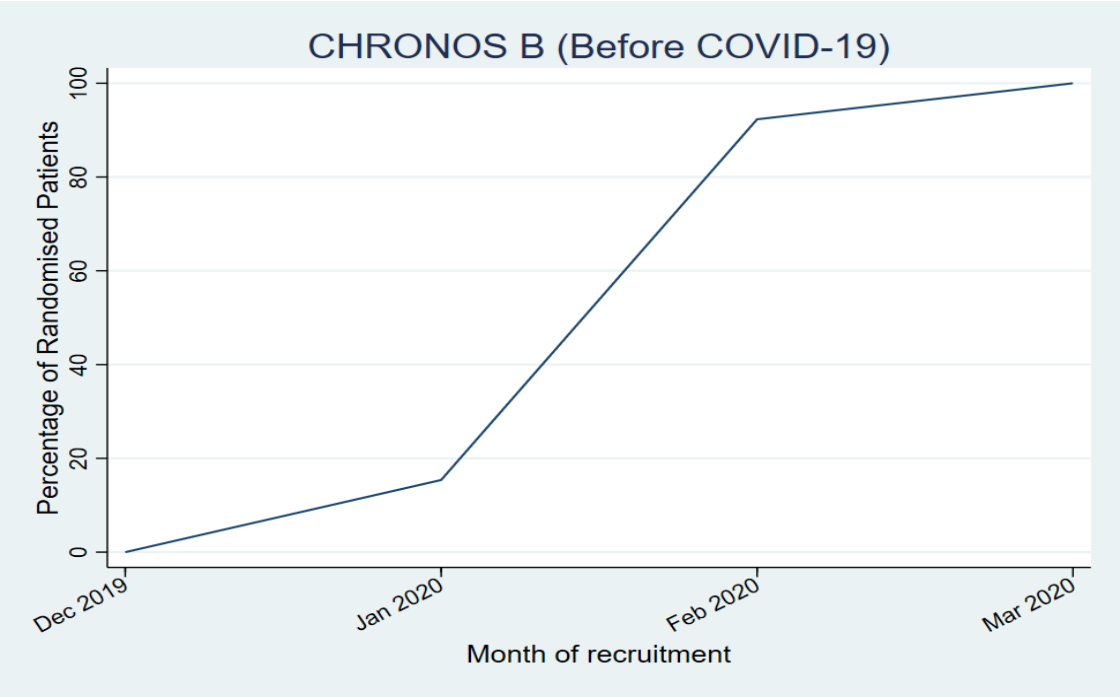


[1]Patients were recruited during/after the Covid-19 pandemic if they were recruited to CHRONOS-B after 05/03/2020 (see Section 9.1)

- **Graph displaying randomisation rate over time (CHRONOS-A), for patients recruited to the trial before[1] the Covid-19 pandemic**

This graph was omited since all patients were recruited during/after the Covid-19 pandemic.

Figure 27: Graph displaying randomisation rate over time (CHRONOS-B), for patients recruited to the trial before[1] the Covid-19 pandemic

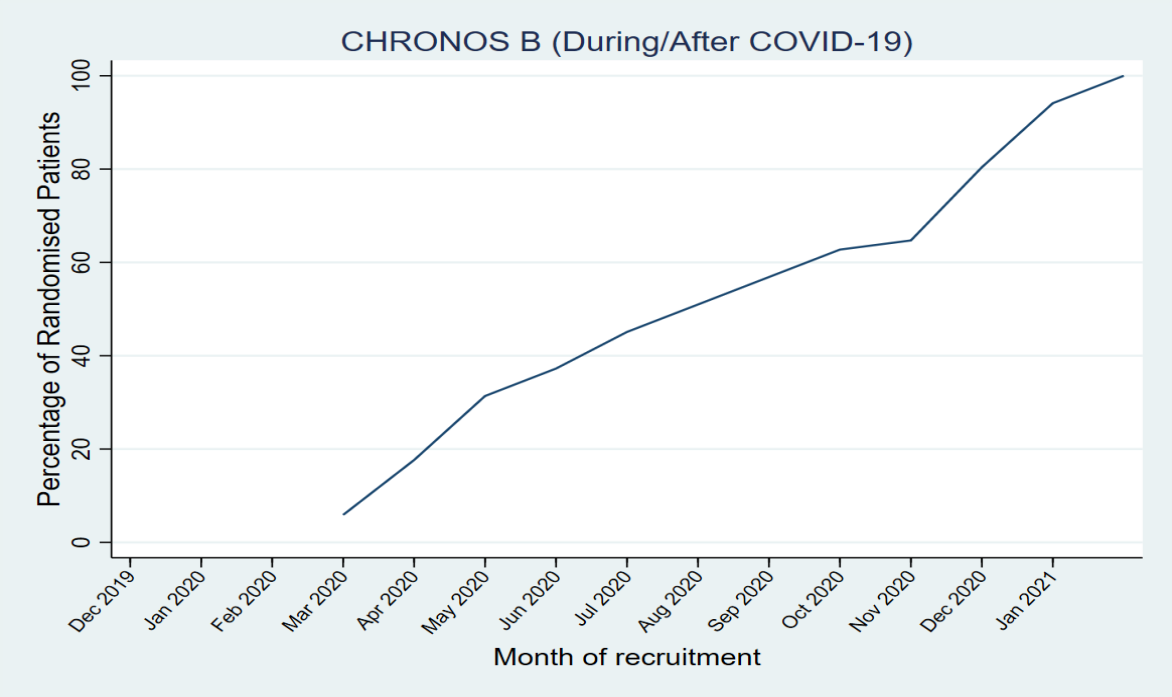


[1]Patients were recruited before the Covid-19 pandemic if they were recruited to the trial before 05/03/2020 (see Section 9.1)

- **Graph displaying randomisation rate over time (CHRONOS-A), for patients recruited to the trial during/after[1] the Covid-19 pandemic**

This graph was omited as Figure 4 displays same information, since the patients were recruited during/after the Covid-19 pandemic.

Figure 28: Graph displaying randomisation rate over time (CHRONOS-B), 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 CHRONOS-B after 05/03/2020 (see Section 9.1)

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)

	Recruitment Rate	Randomisation Rate
CHRONOS-A[3]	17.5% (37/211)	97.3% (36/37)
95% CI	12.7% to 23.4%	85.8% to 99.9%
CHRONOS-B	43.2% (51/118)	100.0% (51/51)
95% CI	34.1% to 52.7%	93% to 1*

[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 9.1)
[3]Results are the same as Table 2.3 as patients were recruited and randomised during//after COVID-19 pandemic period
(*) one-sided, 97.5% confidence interval

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

No data

[1]Patients were recruited before the Covid-19 pandemic if they were recruited to the trial before 05/03/2020 (see Section 9.1)

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

No data

[1]Patients were recruited during/after the Covid-19 pandemic if they were recruited to the trial after 05/03/2020 (see Section 9.1)

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

No data

[1]Patients were recruited before the Covid-19 pandemic if they were recruited to the trial before 05/03/2020 (see Section 9.1)

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)

No data

[1]Patients were recruited during/after the Covid-19 pandemic if they were recruited to the trial after 05/03/2020 (see Section 9.1)

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).

No data

[1]Patients were recruited before the Covid-19 pandemic if they were recruited to CHRONOS-A before 05/03/2020 (see Section 9.1)

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)

This table was omited as Table 2.4 shows the same information in the section of consent-Randomisation, since the patients were recruited during/after 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 9.1)

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)

No data

[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 9.1)

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)

This table was omited as Table 2.4 shows same information in the section of Randomisation-Treatment, since the patients were recruited during/after 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 9.1)

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 + finasteride N=4	Focal + bicalutamide N=4	Focal alone N=5	Total N=13
Consent-Randomisation	N	4	4	5	13
	Min	0	0	0	0
	Mean (SD)	0 (0)	0 (0)	3 (6.71)	1.15 (4.16)
	Median (IQR)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
	Max	0	0	15	15
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[1]Patients were recruited before the Covid-19 pandemic if they were recruited to CHRONOS-B before 05/03/2020 (see Section 9.1)

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)

Time between (Days)	Statistics	Focal + finasteride N=17	Focal + bicalutamide N=17	Focal alone N=17	Total N=51
Consent-Randomisation	N	17	17	17	51
	Min	0	0	0	0
	Mean (SD)	1.94 (3.21)	2.65 (4.27)	2.29 (3.51)	2.29 (3.63)
	Median (IQR)	0 (0 to 2)	1 (0 to 2)	0 (0 to 3)	1 (0 to 3)
	Max	11	16	12	16
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[1]Patients were recruited during/after the Covid-19 pandemic if they were recruited to CHRONOS-B on/after 05/03/2020 (see Section 9.1)

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 + finasteride N=4	Focal + bicalutamide N=4	Focal alone N=5	Total N=13
Randomisation-Treatment	N	4	4	5	13
	Min	85	91	13	13
	Mean (SD)	109.25 (33.61)	116.75 (17.59)	73.6 (42.41)	97.85 (36.97)
	Median (IQR)	96.5 (90.5 to 128)	123.5 (105.5 to 128)	78 (57 to 93)	96 (85 to 127)
	Max	159	129	127	159
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Randomisation-Neoadjuvant Drug Treatment	N	4	4		8
	Min	0	0		0
	Mean (SD)	0 (0)	0.5 (1)		0.25 (0.71)
	Median (IQR)	0 (0 to 0)	0 (0 to 1)	-	0 (0 to 0)
	Max	0	2		2
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)		5 (38.5%)
Start of Neoadjuvant Drug Treatment - Focal Therapy	N	4	4		8
	Min	85	91		85
	Mean (SD)	109.25 (33.61)	116.25 (17.15)		112.75 (24.98)
	Median (IQR)	96.5 (90.5 to 128)	123.5 (105.5 to 127)	-	108.5 (93.5 to 127)
	Max	159	127		159
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)		5 (38.5%)

[1]Patients who underwent treatment before the Covid-19 pandemic if they had a focal treatment date before 05/03/2020 (see Section 9.1)

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)

Time between (Days)	Statistics	Focal + finasteride N=17	Focal + bicalutamide N=17	Focal alone N=17	Total N=51
Randomisation-Treatment	N	17	17	17	51
	Min	81	86	2	2
	Mean (SD)	116.12 (40.5)	113.76 (55.06)	67.06 (45.65)	98.98 (51.8)
	Median (IQR)	103 (87 to 119)	102 (92 to 109)	69 (20 to 87)	93 (84 to 110)
	Max	208	324	155	324
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Randomisation-Neoadjuvant Drug Treatment	N	17	17		34
	Min	0	0		0
	Mean (SD)	7.35 (12.65)	2.88 (4.12)		5.12 (9.54)
	Median (IQR)	1 (0 to 12)	1 (0 to 5)	-	1 (0 to 6)
	Max	49	15		49
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)		17 (33.3%)
Start of Neoadjuvant Drug Treatment - Focal Therapy	N	17	17		34
	Min	36	71		36
	Mean (SD)	108.76 (43.15)	110.88 (55.65)		109.82 (49.05)
	Median (IQR)	102 (85 to 118)	98 (92 to 106)	-	98.5 (86 to 117)
	Max	193	322		322
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)		17 (33.3%)

[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 9.1)

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

No data

[1]Patients are expected to have reached Visit 3 by the end of the feasibility phase
[2]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 9.1)

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

Same values than Table 2.6 as patients were recruited and randomised during/after the Covid-19 pandemic.

[1]Patients are expected to have reached Visit 3 by the end of the feasibility phase
[2]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 9.1)

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

Visits[3]	Statistics	Focal + finasteride N=4	Focal + bicalutamide N=4	Focal alone N=5	Total N=13
Screening Visit1 – Visit 2	N	4	4	5	13
	Min	85	91	13	13
	Mean (SD)	109.25 (33.61)	116.75 (17.59)	73.6 (42.41)	97.85 (36.97)
	Median (IQR)	96.5 (90.5 to 128)	123.5 (105.5 to 128)	78 (57 to 93)	96 (85 to 127)
	Max	159	129	127	159
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 2 – Visit 3	N	4	4	5	13
	Min	43	88	88	43
	Mean (SD)	118.25 (66.06)	96.25 (10.4)	92.4 (3.65)	101.54 (35.49)
	Median (IQR)	116 (68 to 168.5)	93 (89 to 103.5)	92 (90 to 95)	93 (90 to 97)
	Max	198	111	97	198
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 3 – Visit 4	N	4	4	5	13
	Min	193	279	281	193
	Mean (SD)	268.75 (54.54)	294.25 (14.73)	306.4 (30.2)	291.08 (37)
	Median (IQR)	280 (233 to 304.5)	292 (284 to 304.5)	296 (285 to 315)	289 (281 to 314)
	Max	322	314	355	355
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 4 – Visit 5	N	4	4	4	12
	Min	108	189	63	63
	Mean (SD)	175.75 (75.56)	230 (50.8)	160 (73.22)	188.58 (68.58)
	Median (IQR)	164.5 (113.5 to 238)	213.5 (199 to 261)	172 (106 to 214)	202 (134 to 225.5)
	Max	266	304	233	304
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	1 (20%)	1 (7.7%)
Visit 5 – Visit 6	N	4	3	4	11
	Min	91	91	91	91
	Mean (SD)	206.5 (100.71)	123.67 (35.23)	198.5 (90.59)	181 (84.39)
	Median (IQR)	217 (122.5 to 290.5)	119 (91 to 161)	196 (136.5 to 260.5)	161 (91 to 280)
	Max	301	161	311	311
	Missing from eCRF – n (%)	0 (0.0%)	1 (25%)	2 (40%)	2 (15.4%)

[1]Patients are expected to have reached Visit 3 by the end of the feasibility phase
[2]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 9.1)
[3]Ten patients have reached Visit 7, three in the Focal +Finasteride arm, three in the Focal+bicalutamide arm and four in the Focal alone arm.

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

Visits[3]	Statistics	Focal + finasteride N=17	Focal + bicalutamide N=17	Focal alone N=17	Total N=51
Screening Visit1 – Visit 2	N	17	17	17	51
	Min	81	61	2	2
	Mean (SD)	117.29 (41.2)	116.94 (57.07)	67.82 (44.84)	100.69 (52.72)
	Median (IQR)	103 (87 to 123)	102 (92 to 119)	69 (21 to 87)	93 (84 to 119)
	Max	208	324	155	324
	Missing from eCRF – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 2 – Visit 3	N	15	16	17	48
	Min	60	66	57	57
	Mean (SD)	94 (29.77)	103.19 (20.74)	98.82 (25.47)	98.77 (25.22)
	Median (IQR)	92 (80 to 98)	97 (91.5 to 109)	94 (86 to 106)	95.5 (88 to 105)
	Max	191	143	161	191
	Missing from eCRF – n (%)	2 (11.8%)	1 (5.9%)	0 (0.0%)	3 (5.9%)
Visit 3 – Visit 4	N	14	16	17	47
	Min	84	210	191	84
	Mean (SD)	278.43 (61.84)	266.06 (23.68)	268.82 (36.66)	270.74 (41.93)
	Median (IQR)	286.5 (266 to 310)	272 (249 to 283.5)	268 (238 to 299)	273 (252 to 299)
	Max	355	299	323	355
	Missing from eCRF – n (%)	3 (17.6%)	1 (5.9%)	0 (0.0%)	4 (7.8%)
Visit 4 – Visit 5	N	14	16	16	46
	Min	63	98	49	49
	Mean (SD)	190.14 (48.55)	195.19 (40.93)	178.88 (51.96)	187.98 (46.78)
	Median (IQR)	196 (182 to 217)	185 (171 to 224)	183 (157.5 to 213)	185 (167 to 224)
	Max	273	260	257	273
	Missing from eCRF – n (%)	3 (17.6%)	1 (5.9%)	1 (5.9%)	5 (9.8%)
Visit 5 – Visit 6	N	8	8	8	24
	Min	50	77	0	0
	Mean (SD)	182.25 (76.33)	141.5 (41.67)	167.75 (92.95)	163.83 (72.31)
	Median (IQR)	185.5 (136.5 to 245)	161 (106 to 171.5)	175 (121 to 217.5)	168 (121.5 to 199.5)
	Max	274	178	315	315
	Missing from eCRF – n (%)	9 (52.9%)	9 (52.9%)	9 (52.9%)	27 (52.9%)

[1]Patients are expected to have reached Visit 3 by the end of the feasibility phase
[2]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 9.1)
[3]Two patients have reached visit 7, one in the Focal + Finasteride arm and one in Focal alone arm.

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)

No data

[1]Patients underwent the visit before the Covid-19 pandemic if the date of visit was before 05/03/2020 (see Section 9.1)

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)

Visit[2]	n (%)	Focal	Radical	Total
Screening visit	Total	18	18	36
	On time	18 (100.0%)	18 (100.0%)	36 (100.0%)
	Early	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Delayed	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 2	Total	18	18	36
	On time	17 (94.4%)	15 (83.3%)	32 (88.9%)
	Early	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Delayed	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Withdrawn	0 (0.0%)	2 (11.1%)	2 (5.6%)
	Missing	1 (5.6%)	1 (5.6%)	2 (5.6%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 3	Total	18	18	36
	On time	13 (72.2%)	6 (33.3%)	19 (52.8%)
	Early	2 (11.1%)	4 (22.2%)	6 (16.7%)
	Delayed	2 (11.1%)	3 (16.7%)	5 (13.9%)
	Withdrawn	0 (0.0%)	4 (22.2%)	4 (11.1%)
	Missing	1 (5.6%)	0 (0.0%)	1 (2.8%)
	Not Applicable	0 (0.0%)	1 (5.6%)	1 (2.8%)

[1]Patients underwent the visit during/after the Covid-19 pandemic if the date of visit was on/after 05/03/2020 (see Section 9.1)
[2]Patients are expected to have reached Visit 43 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]	n (%)	Focal + finasteride	Focal + bicalutamide	Focal alone	Total
Screening visit	Total	4	4	5	13
	On time	4 (100.0%)	4 (100.0%)	5 (100.0%)	13 (100.0%)
	Early	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Delayed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 2	Total	4	4	5	13
	On time	4 (100.0%)	4 (100.0%)	5 (100.0%)	13 (100.0%)
	Early	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Delayed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 3	Total	4	4	5	13
	On time	1 (25.0%)	4 (100.0%)	5 (100.0%)	10 (76.9%)
	Early	1 (25.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	Delayed	2 (50.0%)	0 (0.0%)	0 (0.0%)	2 (15.4%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 4	Total	4	4	5	13
	On time	3 (75.0%)	3 (75.0%)	3 (60.0%)	9 (69.2%)
	Early	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Delayed	1 (25.0%)	1 (25.0%)	2 (40.0%)	4 (30.8%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 5	Total	4	4	5	13
	On time	2 (50.0%)	1 (25.0%)	2 (40.0%)	5 (38.5%)
	Early	1 (25.0%)	0 (0.0%)	1 (20.0%)	2 (15.4%)
	Delayed	1 (25.0%)	3 (75.0%)	1 (20.0%)	5 (38.5%)
	Withdrawn	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (7.7%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 6	Total	4	4	5	13
	On time	2 (50.0%)	3 (75.0%)	1 (20.0%)	6 (46.2%)
	Early	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (7.7%)
	Delayed	2 (50.0%)	0 (0.0%)	2 (40.0%)	4 (30.8%)
	Withdrawn	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (7.7%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (7.7%)

[1]Patients underwent the visit before the Covid-19 pandemic if the date of visit was before 05/03/2020 (see Section 9.1)
[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)

Visit[2]	n (%)	Focal + finasteride	Focal + bicalutamide	Focal alone	Total
Screening visit	Total	17	17	17	51
	On time	17 (100.0%)	17 (100.0%)	17 (100.0%)	51 (100.0%)
	Early	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Delayed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 2	Total	17	17	17	51
	On time	17 (100.0%)	17 (100.0%)	17 (100.0%)	51 (100.0%)
	Early	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Delayed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 3	Total	17	17	17	51
	On time	13 (76.5%)	13 (76.5%)	14 (82.4%)	40 (78.4%)
	Early	1 (5.9%)	0 (0.0%)	1 (5.9%)	2 (3.9%)
	Delayed	1 (5.9%)	3 (17.6%)	2 (11.8%)	6 (11.8%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	2 (11.8%)	1 (5.9%)	0 (0.0%)	3 (5.9%)
	Not Applicable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 4	Total	17	17	17	51
	On time	13 (76.5%)	12 (70.6%)	14 (82.4%)	39 (76.5%)
	Early	1 (5.9%)	3 (17.6%)	2 (11.8%)	6 (11.8%)
	Delayed	2 (11.8%)	2 (11.8%)	1 (5.9%)	5 (9.8%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Visit 5	Total	17	17	17	51
	On time	5 (29.4%)	9 (52.9%)	9 (52.9%)	23 (45.1%)
	Early	4 (23.5%)	2 (11.8%)	4 (23.5%)	10 (19.6%)
	Delayed	5 (29.4%)	5 (29.4%)	3 (17.6%)	13 (25.5%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not Applicable	3 (17.6%)	1 (5.9%)	1 (5.9%)	5 (9.8%)
Visit 6	Total	17	17	17	51
	On time	7 (41.2%)	6 (35.3%)	3 (17.6%)	16 (31.4%)
	Early	1 (5.9%)	2 (11.8%)	4 (23.5%)	7 (13.7%)
	Delayed	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (2.0%)
	Withdrawn	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	1 (5.9%)	0 (0.0%)	1 (5.9%)	2 (3.9%)
	Not Applicable	8 (47.1%)	9 (52.9%)	8 (47.1%)	25 (49.0%)

[1]Patients underwent the visit during/after the Covid-19 pandemic if the date of visit was on/after 05/03/2020 (see Section 9.1)
[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

No data

[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 9.1)

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

Treatment compliance	Focal (N=18)	Radical (N=18)	Total (N=36)
Underwent treatment– n(%) 95% CI	16 (88.9%) 65.3% to 98.6%	13 (72.2%) 46.5% to 90.3%	29 (80.6%) 64% to 91.8%
Withdrawal – n (%)	0 (0.0%)	4 (22.2%)	4 (11.1%)
Screening failure– n (%)	1 (5.6%)	0 (0.0%)	1 (2.8%)

[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 9.1)

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

Treatment compliance	Focal + finasteride (N=4)	Focal + bicalutamide (N=4)	Focal alone (N=5)	Total (N=13)
Underwent treatment – n (%) 95% CI	4 (100.0%) 39.8% to 1*	4 (100.0%) 39.8% to 1*	5 (100.0%) 47.8% to 1*	13 (100.0%) 75.3% to 1*
Withdrawal – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[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 9.1)
(*) one-sided, 97.5% confidence interval

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

Treatment compliance	Focal + finasteride (N=17)	Focal + bicalutamide (N=17)	Focal alone (N=17)	Total (N=51)
Underwent treatment – n (%) 95% CI	17 (100.0%) 80.5% to 1*	17 (100.0%) 80.5% to 1*	17 (100.0%) 80.5% to 1*	51 (100.0%) 93% to 1*
Withdrawal – n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[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 9.1)
(*) one-sided, 97.5% confidence interval

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

Drug compliance	Focal + finasteride (N=4)	Focal + bicalutamide (N=4)	Focal alone	Total (N=8)
Returned empty blister packs[2] – n(%) 95% CI	1 (25.0%) 14.6% to 57%	1 (25.0%) 8.2% to 47.2%	- -	2 (25.0%) 15.7% to 44.6%
Patients who were given the drug and did not have a registered protocol deviation[3]– n (%) 95% CI	4 (100.0%) 83.9% to 1*	4 (100.0%) 83.9% to 1*	- -	8 (100.0%) 84.6% to 1*

[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 9.1)
(*) one-sided, 97.5% confidence interval

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

Drug compliance	Focal + Finasteride (N=17)	Focal + Bicalutamide (N=17)	Focal alone	Total (N=34)
Returned empty blister packs[2] – n(%) 95% CI	6 (35.3%) 14.6% to 57%	4 (23.5%) 8.2% to 47.2%	- -	10 (29.4%) 15.7% to 44.6%
Patients who were given the drug and did not have a registered protocol deviation[3]– n (%) 95% CI	17 (100.0%) 83.9% to 1*	17 (100.0%) 83.9% to 1*	- -	34 (100.0%) 84.6% to 1*

[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 9.1)
(*) one-sided, 97.5% confidence interval

11. Post Hoc Analysis

Table 7. 1: Treatment compliance (CHRONOS-A) by treatment arm and by specific focal treatment received

Treatment arm	Treatment Compliance	Received Focal therapy			
		Cryotherapy	HIFU	Screening failure	Total
focal	No	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (5.6%)
	Yes	13 (100.0%)	3 (75.0%)	0 (0.0%)	16 (88.9%)
	Withdrawal	-	-	-	-
	Screening failure	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (5.6%)
Treatment arm	**Treatment Compliance**	**Received Radical therapy**			
		Prostatectomy	**Radio/Brachytherapy**	**Withdrawal**	**Total**
Radical	No	1 (20.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
	Yes	4 (80.0%)	9 (100.0%)	0 (0.0%)	13 (72.2%)
	Withdrawal	0 (0.0%)	0 (0.0%)	4 (100.0%)	4 (22.2%)
	Screening failure	-	-	-	-

Table 7. 2: Treatment compliance (CHRONOS-B) by treatment arm and by specific focal treatment received

Treatment arm	Treatment Compliance	Received Focal therapy			
		Cryotherapy	HIFU	Screening failure	Total
Focal + finasteride	No	-	-	-	-
	Yes	4 (100.0%)	17 (100.0%)	-	21 (100.0%)
	Withdrawal	-	-	-	-
	Screening failure	-	-	-	-
Focal + bicalutamide	No	-	-	-	-
	Yes	8 (100.0%)	13 (100.0%)	-	21 (100.0%)
	Withdrawal	-	-	-	-
	Screening failure	-	-	-	-
Focal alone	No	-	-	-	-
	Yes	6 (100.0%)	16 (100.0%)	-	22 (100.0%)
	Withdrawal	-	-	-	-
	Screening failure	-	-	-	-

12. 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.

13. Deviation/Amendments from SAP

1. The CONSORT Diagrams CHRONOS A and CHRONOS B (**Figures 1 and Figure 2**) in the Final Statistical report were modified from the SAP to include the information that was collected and provided by the Trial Manager:

    - The number of patients approached
    - Reasons and number of patients not eligible
    - Reasons and number of patients who declined consent

    Instead of what was specified in the SAP:

    - Number of patients assessed for eligibility
    - Number and reasons of patients excluded
    - Number and reasons of patients who withdrew.

2. In the Final Statistical Report, **Table 1.1, Table 1.5, Table 2.13 to Table 2.16** Baseline Characteristics for CHRONOS A and CHRONOS B were modified to remove the row of "missing from eCRF" as this category reports the same information as "not reported".

3. In the **Table 1.2 and Table 1.6** summarising the IPSS Questionnaires at baseline (Visit 1) for CHRONOS A and CHRONOS B were modified to add the category of Missing from eCRF as this category is needed to classify all the possible outcomes of Severity.

4. The number of patients (recruited and randomised) and period of recruitment in months by centre for CHRONOS A and CHRONOS B were included in the **Table 2.2** to providing extra clarification of how the mean number of patients per month was obtained.

In the section 8.3 Figures to present.

5. The Graphs displaying recruitment rate over time for CHRONOS A and CHRONOS B were omitted because the calculation of the recruitment rate by month requires data on number of patients approached stratified both by month and by site, but this information was only collected by site.

6. The Graph displaying actual vs target recruitment rate over time for CHRONOS A was modified to show the number of recruited patients of the original predicted target, the adjusted target, and the actual recruitment my month instead of only present the actual and target recruitment rate (**Figure 2**).

7. **Figure 6** and **Figure 7** were added to the report as these graphs were presented by the Trial manager to report the number of patients recruited month by month and show the period of before and after COVID. Although Figure 2 and Figure 3 display the same information as Figure 6 and Figure 7, they show a discrepancy as Figure 6 and Figure 7 were not created using the exact dates and the information of the database.

8. The histograms described in the SAP for the PROMS Q-5D-5L, EQ VAS, IIEF15, EPIC-26 and EPIC-URINARY DOMAIN were modified to show change in mean scores for individual domains (and corresponding 95% confidence intervals) from randomisation to 3 months for CHRONOS A and from randomisation to 12 months for CHRONOS B following the suggestion of the CI.

9. The **Table A1** and **Table A2** presenting the summary of recruitment and randomisation by site (CHRONOS A and CHRONOS B) were added to the report to show when each site was open, when the site pauses recruitment if any, the number of patients recruited by month and the final number of patients recruited and randomised.

10. The **Table 2.4** presenting the summary statistics for time between consent and randomisation (Days), and between randomisation and treatment (Days), by treatment arm (CHRONOS-A) was modified to add the categories of Min and Max to provide extra information.

11. The **Table 2.5** presenting 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) was modified to add the categories of Min and Max to provide extra information.

12. The **Table 2.6** presenting the summary statistics of time between consecutive visits (Days) from Screening Visit 1 to Visit 4[1], by treatment arm (CHRONOS-A) was expanded to include the information for Visit 3 – Visit 4 as some patients have reached this time visit.

13. The **Table 2.7** presenting the summary statistics of time between consecutive visits (Days) from Screening Visit 1 to Visit 4[1], by treatment arm (CHRONOS-B) was expanded to include the information for Visit 3 – Visit 4, Visit 4 – Visit 5 and Visit 5 – Visit 6 as the following period for some patients have reached this time visits.

14. The **Table 2.8** presenting the treatment compliance (CHRONOS-A)[1], and corresponding 95% confidence intervals and the **Table 2.9** presenting the treatment compliance (CHRONOS-B)[1], and corresponding 95% confidence intervals were modified to add the number of withdrawals.

15. The **Table 2.11** presenting the reasons for ineligibility (CHRONOS-A and CHRONOS-B) is not presented as only one case (CHR12-085) was recorded in Inform database who failed inclusion. The reason given was "Screening Failure".

16. The **Table 2.15** presenting the Baseline characteristics, by treatment arm, for patients who withdrew from CHRONOS-B is not presented as only one patient withdrew from CHRONOS B.

17. **Table 2.21** presenting Summary of Serious Adverse Events by Category, by Treatment Arm was modified to include the “Total” column because the other tables of Adverse Events report the “Total” column.

18. **Table 2.23 through 2.28** were added to report the Adverse Events and Serious Adverse Events for CHRONOS B as the SAP specified that they should be reported separately from CHRONOS A (see **Tables 2.17 to Table 2.22**).

In the section 8.4 Analysis of Secondary End Points.

The tables presenting the summary statistics for the PROMS **Q-5D-5L, EQ VAS, IIEF15, EPIC-26 and EPIC-URINARY DOMAIN** for CHRONOS A have been expanded from **Table 3.1 - 3.5 to Table 3.1 - 3.10** to include all the tables needed to display the information for visit 1 and visit 3 for each PROM.

The tables presenting the summary statistics for the PROMS **Q-5D-5L, EQ VAS, IIEF15, EPIC-26 and EPIC-URINARY DOMAIN** for CHRONOS B have been expanded from **Table 3.6 - 3.10 to Table 3.11 - 3.25** to include all the tables needed to display the information for visit 1, visit 3 and visit 4 for each PROM.

19. The **Table 3.1 (visit 1) and Table 3.2 (visit 3)** presenting the Summary statistics of EQ-5D-5L[1] dimensions and levels, by treatment arm for CHRONOS-A and the **Table 3.11 (visit 1), Table 3.12 (visit 3) and Table 3.13 (visit 4)** for CHRONOS-B were modified to add the category of Missing from eCRF as this category is needed to classify all the possible outcomes.

20. The **Table 3.3 (visit 1) and Table 3.4 (visit 3)** presenting the Summary statistics for EQ VAS (EQ-5D-5L)[1], by treatment arm (CHRONOS-A) and the **Table 3.14 (visit 1), Table 3.15 (visit 3)**

and Table 3.16 (visit 4) for CHRONOS-B were modified to add the categories of Min and Max to provide extra information to the table.

21. The **Table 3.5 (visit 1) and Table 3.6 (visit 3)** presenting the Summary statistics of IIEF15[1] domains, by treatment arm (CHRONOS-A) and the **Table 3.17 (visit 1), Table 3.18 (visit 3) and Table 3.19 (visit 4)** for CHRONOS-B were modified to add the categories of Min, Max and Ungradable to provide extra information to the table.

22. The **Table 3.7 (visit 1) and Table 3.8 (visit 3)** presenting the Summary statistics of EPIC-26[1] domains, by treatment arm (CHRONOS-A) and the **Table 3.20 (visit 1), Table 3.21 (visit 3) and Table 3.22 (visit 4)** for CHRONOS-B were modified to add the categories of Min, Max and Ungradable to provide extra information to the table.

23. The **Table 3.9 (visit 1) and Table 3.10 (visit 3)** presenting the Summary statistics of EPIC-URINARY DOMAIN[1] subscales, by treatment arm (CHRONOS-A) and the **Table 3.23 (visit 1), Table 3.24 (visit 3) and Table 3.25 (visit 4)** for CHRONOS-B were modified to add the categories of Min, Max and Ungradable to provide extra information to the table.

In section 8.4.1 Protocol Deviations/Violations

24. **Tables 4.3 and 4.4** were added to report on Protocol Deviations and Violations for CHRONOS B as the SAP specified for these to be reported separately from CHRONOS A (see **Tables 4.1 to Table 4.2**).

In the section 10 in tables to present the Impact of the Covid-19 Pandemic in CHRONOS A and CHRONOS B.

25. The **Table 5.1** presenting the Baseline characteristics, by treatment arm, for patients recruited to the trial before[1] the Covid-19 pandemic (CHRONOS-A) is not presented as all patients were recruited and randomised during/after COVID-19 pandemic period.

26. The **Table 5.2** presenting the Baseline characteristics, by treatment arm, for patients recruited to the trial during/after[1] the Covid-19 pandemic (CHRONOS-B) is not presented as the result of this table are the same as the Table 1.1 as all patients were recruited and randomised during/after COVID-19 pandemic period.

In the section 10.1 Figures to present (COVID-19)

27. The Graph displaying recruitment rate over time (CHRONOS-A and CHRONOS-B), for patients recruited to the trial **before** the Covid-19 pandemic was omitted because the calculation of the recruitment rate by month requires data on number of patients approached stratified both by month and by site but this information was only collected by site.

28. The Graph displaying recruitment rate over time (CHRONOS-A and CHRONOS-B), for patients recruited to the trial **during/after** the Covid-19 pandemic was omitted because the calculation of the randomisation rate by month requires data on number of patients approached stratified both by month and by site but this information was only collected by site.

29. The Graph displaying **actual vs target** recruitment rate over time for CHRONOS A, for patients recruited to the trial **before**[1] the Covid-19 pandemic was omitted since all patients were recruited during/after the Covid-19 pandemic.

30. The Graph displaying **actual vs target** recruitment rate over time for CHRONOS B, for patients recruited to the trial **before**[1] the Covid-19 pandemic was modified to show the cumulative number of recruited patients of the predicted target and the actual recruitment my month instead of presenting the actual and target recruitment rates (**Figure 25**).

31. The Graph displaying **actual vs target** recruitment rate over time for CHRONOS A, for patients recruited to the trial **during/after**[2] the Covid-19 pandemic was omitted since the graph showed the same results as **Figure 2**.

32. The Graph displaying **actual vs target** recruitment rate over time for CHRONOS B, for patients recruited to the trial **during/after**[2] the Covid-19 pandemic was modified to show the cumulative number of recruited patients of the predicted target and the actual recruitment by month instead of presenting the actual and target recruitment rates (**Figure 26**).

33. The Graph displaying randomisation rate over time for CHRONOS-A, for patients recruited to the trial **before**[1] the Covid-19 pandemic was omitted since all patients were recruited **during/after** the Covid-19 pandemic.

34. The Graph displaying randomisation rate over time (CHRONOS-A), for patients recruited to the trial during/after[1] the Covid-19 pandemic was omitted since the graph showed the same results as **Figure 4**.

35. **Tables 6.5, 6.6,6.7,6.8,6.9,6.11,6.17,6.21,6.25** described in the SAP were not done as there was not data collected.

36. **Table 6.18** described in the SAP was not presented as the results were the same as **Table 2.6**

37. **Tables 6.23 and 6.24** include extra categorisations for On Time, Early, Withdrawn and Not Applicable because these categories are needed to classify all the possible outcomes of visits.

In Section 11 Post Hoc Analysis

38. A post hoc analysis has been requested regarding the treatment compliance by treatment arm and by specific focal treatment received for CHRONOS A and CHRONOS B. **Tables 7.1 and 7.2** have been added to the report. This information is in section 11.

14. References

1. *International Prostate Symptom Score (IPSS) change and changing factor in intensity-modulated radiotherapy combined with androgen deprivation therapy for prostate cancer.* Tomita N., Oze I., Shimizu H., Yoshida M., Kimura K. et al. 77(4), s.l. : Nagoya J Med Sci., 2015. 637-646.

2. 2019, EuroQol Research Foundation. EQ-5D-5L User Guide - Basic information on how to use the EQ-5D-5L instrument. *EuroQol - EQ-5D.* [Online] 3.0, September 2019. [Cited: 27 January 2020.] https://euroqol.org/wp-content/uploads/2019/09/EQ-5D-5L-English-User-Guide_version-3.0-Sept-2019-secured.pdf.

3. *The International Index of Erectile Function (IIEF): A multidimensional scale for assessment of erectile dysfunction.* Rosen R, Riley A, Wagner G, et al. 49, 1997, Urology, pp. 822-830.

4. Sanda MG., Wei JT., Litwin MS. *Scoring Instructions for the Expanded Prostate cancer Index Composite Short Form (EPIC-26).* s.l. : University of Michigan, 2002.

5. England, Public Health. *NOIDs Weekly Report - Statutory Notification of Infectious Diseases in England and Wales Week 2020/10 week ending 08/03/2020.* 2020.