

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Donovan JL, Hamdy FC, Lane JA, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med* 2016;375:1425-37. DOI: 10.1056/NEJMoa1606221

# **Appendix**

## **Supplementary material**

### **Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer ProtecT trial**

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The ProtecT study was designed by FCH, JLD and DEN. Data analysis was designed by CM and TJP, and conducted by CM. All authors contributed to data collection. The data are vouched for by JAL and MD, and the analysis by CM, JAL, MD and TJP. JLD wrote the first draft of the manuscript. The institutions, sponsor and funder had no role in publication. JLD, FCH and DEN decided to publish the paper.

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**Table S1A: Baseline sociodemographic and clinical characteristics by allocated treatment group**

	Active monitoring (n=545)	Prostatectomy (n=553)	Radiotherapy (n=545)
Mean age in years at randomization (SD <sup>1</sup> )	62 (5)	62 (5)	62 (5)
White ethnicity (%)	535 (99)	542 (99)	529 (98)
Married or living with partner (%)	457 (84)	458 (84)	460 (85)
Managerial / professional occupation (%)	229 (43)	229 (42)	226 (42)
Known family history prostate cancer (%)	43 (8)	32 (6)	44 (8)
Median PSA <sup>2</sup> in ng/ml (Inter-quartile range)	4.7 (3.7, 6.7)	4.9 (3.7, 6.7)	4.8 (3.7, 6.7)
Gleason score			
6	421 (77)	422 (76)	423 (78)
7	111 (20)	120 (22)	108 (20)
8-10	13 (2)	10 (2)	14 (3)
Missing	0	1	0
Clinical stage			
T1c	410 (75)	410 (74)	429 (79)
T2	135 (25)	143 (26)	116 (21)

<sup>1</sup> Standard Deviation.

<sup>2</sup> For the large majority of men with PSA measures from the prostate check clinic and prior to biopsy, the mean of these two has been taken.

**Table S1B: Response rates for exemplar outcome measures**

Assessment point	ICIQ score*	EPIC sexual function score*	HADS anxiety
	Complete / expected (%)	Complete / expected (%)	Complete / expected (%)
Baseline	1244/1539 (81%)	726/1011 (72%)	1591/1643 (97%)
6 months	1405/1572 (89%)	1013/1140 (89%)	1428/1638 (87%)
12 months	1377/1612 (85%)	1029/1214 (85%)	1422/1633 (87%)
24 months	1379/1624 (85%)	1131/1362 (83%)	1411/1625 (87%)
36 months	1386/1614 (86%)	1257/1479 (85%)	1410/1614 (87%)
48 months	1383/1602 (86%)	1325/1542 (86%)	1419/1602 (89%)
60 months	1384/1589 (87%)	1367/1587 (86%)	1413/1589 (89%)
72 months	1369/1572 (87%)	1352/1572 (86%)	1388/1572 (88%)

\*ICIQ introduced 1<sup>st</sup> October 2001, EPIC introduced 1<sup>st</sup> March 2005; “expected” counts are the number of men for whom an assessment point falls after the introduction of the stated measure.

**Table S2: Tabular presentation of outcomes in the four key domains of urinary, sexual and bowel function and quality of life, and health-related quality of life**

**Table S2A. Urinary function and impact on quality of life: urinary incontinence scores**

	AM		RP		RT		p-value
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	
<b>ICIQ score</b>							
Baseline	1.3 (2.5)	422	1.3 (2.4)	414	1.2 (2.1)	408	
6 months	2.0 (3.3)	459	5.5 (5.2)	476	2.1 (3.5)	471	
12 months	2.2 (3.2)	465	4.3 (4.2)	460	1.7 (2.7)	457	
24 months	2.2 (3.3)	453	3.9 (4.1)	468	2.0 (2.8)	458	
36 months	2.4 (3.4)	469	4.0 (4.3)	461	2.0 (2.8)	456	
48 months	2.6 (3.5)	463	4.2 (4.1)	462	2.1 (2.9)	458	
60 months	2.5 (3.5)	458	3.8 (3.7)	465	2.1 (2.9)	461	
72 months	2.9 (3.8)	451	4.0 (4.0)	463	2.2 (2.9)	455	<0.001
<b>EPIC urinary incontinence sub-score</b>							
Baseline	93.5 (11.3)	244	92.8 (11.6)	255	92.8 (11.0)	246	
6 months	89.1 (16.0)	345	67.4 (29.1)	361	88.7 (16.8)	338	
12 months	89.1 (15.3)	353	76.5 (23.7)	354	90.5 (13.5)	354	
24 months	88.9 (15.0)	389	80.3 (21.4)	393	89.0 (14.1)	387	
36 months	87.3 (16.7)	426	79.3 (21.8)	425	89.8 (13.5)	417	
48 months	86.8 (17.4)	446	80.2 (20.3)	445	89.2 (14.4)	449	
60 months	87.2 (16.8)	455	80.6 (20.2)	455	89.4 (14.4)	455	
72 months	85.8 (18.5)	446	80.9 (20.2)	449	89.4 (14.0)	443	<0.001
<b>ICSmaleSF urinary incontinence score</b>							
Baseline	1.9 (2.1)	471	1.8 (1.9)	483	1.8 (1.8)	463	
6 months	2.3 (2.7)	470	4.6 (4.1)	485	2.7 (2.5)	477	
12 months	2.3 (2.5)	483	3.8 (3.5)	474	2.1 (2.2)	472	
24 months	2.5 (2.6)	470	3.7 (3.4)	480	2.4 (2.3)	476	
36 months	2.6 (2.6)	478	4.0 (3.7)	467	2.3 (2.2)	466	
48 months	2.8 (2.9)	480	4.0 (3.6)	470	2.5 (2.4)	468	
60 months	2.8 (2.8)	467	3.8 (3.1)	473	2.5 (2.4)	470	
72 months	3.0 (3.1)	461	3.8 (3.1)	465	2.4 (2.4)	465	<0.001

**Table S2A continued. Urinary function and impact on quality of life: Urinary incontinence**

	AM		RP		RT		p-value
	n / N	(%)	n / N	(%)	n / N	(%)	
<b>Completely continent (ICIQ score 0)</b>							
Baseline	305/422	(72.3)	288/414	(69.6)	280/408	(68.6)	
6 months	280/459	(61.0)	138/476	(29.0)	291/471	(61.8)	
12 months	268/465	(57.6)	135/460	(29.4)	281/457	(61.5)	
24 months	249/453	(55.0)	155/468	(33.1)	255/458	(55.7)	
36 months	248/469	(52.9)	146/461	(31.7)	258/456	(56.6)	
48 months	236/463	(51.0)	130/462	(28.1)	255/458	(55.7)	
60 months	244/458	(53.3)	143/465	(30.8)	239/461	(51.8)	
72 months	225/451	(49.9)	145/463	(31.3)	231/455	(50.8)	<0.001
<b>One or more pads per day in past 4 weeks (EPIC item)</b>							
Baseline	1/250	(0.4)	4/256	(1.6)	0/248	(0.0)	
6 months	15/346	(4.3)	165/362	(45.6)	17/343	(5.0)	
12 months	15/357	(4.2)	95/362	(26.2)	13/358	(3.6)	
24 months	15/392	(3.8)	80/399	(20.1)	16/394	(4.1)	
36 months	22/434	(5.1)	85/434	(19.6)	13/430	(3.0)	
48 months	31/455	(6.8)	77/451	(17.1)	16/456	(3.5)	
60 months	32/461	(6.9)	77/459	(16.8)	15/472	(3.2)	
72 months	38/453	(8.4)	79/455	(17.4)	16/452	(3.5)	<0.001
<b>Urinary function and impact on quality of life (QoL): Impact of urinary incontinence on QoL</b>							
	AM		RP		RT		p-value
	n / N	(%)	n / N	(%)	n / N	(%)	
<b>ICIQ: Moderate to large interference (score 4+) versus mild to no interference (score 0-3)</b>							
Baseline	12/428	(2.8)	8/418	(1.9)	9/413	(2.2)	
6 months	18/464	(3.9)	93/480	(19.4)	27/474	(5.7)	
12 months	25/474	(5.3)	56/469	(11.9)	16/462	(3.5)	
24 months	23/458	(5.0)	50/469	(10.7)	20/462	(4.3)	
36 months	32/473	(6.8)	56/465	(12.0)	17/460	(3.7)	
48 months	38/467	(8.1)	51/466	(10.9)	13/459	(2.8)	
60 months	37/460	(8.0)	43/467	(9.2)	20/467	(4.3)	
72 months	38/455	(8.4)	58/464	(12.5)	21/458	(4.6)	<0.001



**Table S2A continued. Urinary function and impact on quality of life: Urinary symptom scores**

	AM		RP		RT		p-value
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	
<b>ICSmaleSF voiding score</b>							
Baseline	3.4 (2.9)	471	3.3 (3.1)	480	3.1 (2.9)	462	
6 months	3.8 (3.4)	473	3.2 (3.2)	483	5.1 (4.1)	476	
12 months	3.7 (3.2)	484	2.8 (2.9)	480	3.1 (2.8)	470	
24 months	3.9 (3.4)	474	2.5 (2.7)	481	3.2 (3.0)	478	
36 months	4.0 (3.3)	481	2.8 (2.9)	475	3.3 (3.0)	472	
48 months	4.0 (3.4)	481	2.8 (2.9)	470	3.3 (2.9)	474	
60 months	4.1 (3.6)	470	2.9 (2.8)	476	3.5 (3.0)	482	
72 months	4.2 (3.6)	464	2.9 (2.9)	469	3.3 (3.0)	468	<0.001
<b>EPIC urinary summary score</b>							
Baseline	93.0 (9.6)	249	91.9 (9.4)	257	93.2 (8.3)	247	
6 months	90.6 (10.7)	347	80.1 (16.6)	364	84.7 (13.8)	343	
12 months	91.2 (10.1)	354	86.5 (13.2)	364	91.9 (9.0)	359	
24 months	90.3 (10.9)	392	88.1 (12.3)	401	91.4 (9.8)	393	
36 months	89.3 (11.5)	433	87.9 (12.1)	433	91.7 (9.2)	425	
48 months	89.2 (12.5)	455	88.6 (11.9)	451	91.4 (9.6)	455	
60 months	89.6 (11.3)	461	88.9 (11.1)	460	91.3 (9.6)	469	
72 months	89.0 (12.5)	454	88.7 (11.3)	455	91.4 (9.2)	452	<0.001
<b>EPIC urinary bother sub-score</b>							
Baseline	91.2 (12.3)	250	89.9 (12.2)	256	92.1 (10.3)	246	
6 months	89.0 (12.9)	345	81.4 (17.4)	364	80.4 (17.5)	342	
12 months	90.0 (12.2)	354	87.7 (14.1)	365	90.6 (11.0)	359	
24 months	88.6 (13.5)	390	88.9 (13.8)	399	90.3 (11.8)	391	
36 months	87.5 (14.1)	433	88.7 (13.4)	434	90.3 (11.4)	426	
48 months	87.9 (14.6)	458	89.5 (13.0)	445	90.4 (11.6)	457	
60 months	88.3 (13.5)	460	89.9 (11.9)	457	90.2 (11.6)	467	
72 months	88.0 (13.9)	457	89.7 (11.9)	453	90.3 (11.2)	452	0.095
<b>EPIC urinary obstruction/irritative sub-score</b>							
Baseline	93.2 (9.5)	249	92.0 (9.9)	257	93.8 (7.9)	247	
6 months	92.0 (9.6)	347	88.7 (12.3)	364	84.3 (15.3)	343	
12 months	92.9 (9.0)	354	92.8 (9.2)	364	93.2 (7.9)	358	
24 months	91.7 (9.9)	392	93.4 (8.7)	402	93.4 (8.5)	393	
36 months	91.1 (10.0)	433	93.3 (8.7)	433	93.3 (7.7)	425	
48 months	91.3 (11.2)	456	94.1 (8.6)	451	93.2 (8.4)	455	
60 months	91.7 (9.8)	461	94.1 (7.6)	461	93.0 (8.3)	469	
72 months	91.5 (11.0)	454	93.7 (7.9)	454	93.1 (7.7)	452	0.77

**Table S2A continued. Urinary function and impact on quality of life: Urinary symptom items**

	AM		RP		RT		p-value
	n / N	(%)	n / N	(%)	n / N	(%)	
<b>ICSmaleSF nocturia item: twice or more per night</b>							
Baseline	125/539	(23.0)	127/547	(23.2)	104/537	(19.4)	
6 months	144/470	(30.6)	192/489	(39.3)	282/478	(59.0)	
12 months	138/481	(28.7)	127/476	(26.7)	154/473	(32.6)	
24 months	148/469	(31.6)	106/481	(22.0)	142/474	(30.0)	
36 months	164/478	(34.3)	117/470	(24.9)	144/465	(31.0)	
48 months	162/475	(34.1)	124/473	(26.2)	155/472	(32.9)	
60 months	174/466	(37.3)	114/474	(24.1)	169/467	(36.2)	
72 months	188/464	(40.5)	126/466	(27.0)	159/464	(34.3)	<0.001
<b>ICSmaleSF daytime frequency more frequent than once every three hours</b>							
Baseline	164/538	(30.5)	179/548	(32.7)	173/537	(32.2)	
6 months	165/473	(34.9)	222/487	(45.6)	261/474	(55.1)	
12 months	156/483	(32.3)	187/477	(39.2)	154/470	(32.8)	
24 months	161/469	(34.3)	156/480	(32.5)	162/473	(34.3)	
36 months	157/479	(32.8)	165/468	(35.3)	152/465	(32.7)	
48 months	167/476	(35.1)	146/469	(31.1)	157/472	(33.3)	
60 months	159/459	(34.6)	161/473	(34.0)	149/471	(31.6)	
72 months	162/460	(35.2)	151/464	(32.5)	154/463	(33.3)	0.47
<b>ICSmaleSF 'somewhat / a lot' of impact of lower urinary tract symptoms on quality of life versus 'not at all / a little'</b>							
Baseline	20/538	(3.7)	10/548	(1.8)	18/539	(3.3)	
6 months	27/474	(5.7)	84/490	(17.1)	60/479	(12.5)	
12 months	26/482	(5.4)	41/477	(8.6)	14/473	(3.0)	
24 months	32/471	(6.8)	39/481	(8.1)	17/473	(3.6)	
36 months	35/482	(7.3)	51/470	(10.6)	20/467	(4.3)	
48 months	40/478	(8.4)	37/474	(7.8)	20/472	(4.2)	
60 months	34/470	(7.2)	30/475	(6.3)	17/474	(3.6)	
72 months	37/465	(8.0)	43/470	(9.2)	21/465	(4.5)	<0.001

**Table S2B. Sexual function and impact on quality of life: Erectile dysfunction items**

	AM		RP		RT		p-value
	n / N	(%)	n / N	(%)	n / N	(%)	
<b>EPIC: Erections firm enough for intercourse</b>							
Baseline	164/243	(67.5)	161/245	(65.7)	169/247	(68.4)	
6 months	173/375	(51.6)	43/359	(12.0)	75/338	(22.2)	
12 months	167/340	(49.1)	52/356	(14.6)	132/351	(37.6)	
24 months	178/378	(47.1)	74/391	(18.9)	132/388	(34.0)	
36 months	173/421	(41.1)	89/427	(20.8)	143/420	(34.0)	
48 months	163/442	(36.9)	90/447	(20.1)	142/447	(31.8)	
60 months	157/449	(35.0)	94/464	(20.3)	125/462	(27.1)	
72 months	134/452	(29.6)	76/461	(16.5)	125/456	(27.4)	<0.001
<b>EPIC: Moderate or big problem with erectile dysfunction</b>							
Baseline	39/239	(16.3)	40/247	(16.2)	39/245	(15.9)	
6 months	97/331	(29.3)	234/354	(66.1)	160/333	(48.0)	
12 months	98/338	(29.0)	222/359	(61.8)	135/346	(39.0)	
24 months	129/375	(34.4)	227/395	(57.5)	138/377	(36.6)	
36 months	157/414	(37.9)	208/421	(49.4)	166/420	(39.5)	
48 months	159/440	(36.1)	226/448	(50.4)	171/449	(38.1)	
60 months	167/443	(37.7)	215/460	(46.7)	170/462	(36.8)	
72 months	174/437	(39.8)	227/457	(49.7)	162/447	(36.2)	<0.001

**Table S2B. Sexual function and impact on quality of life**

	AM		RP		RT		p-value
	n / N	(%)	n / N	(%)	n / N	(%)	
<b>EPIC sexual summary score</b>							
Baseline	60.3 (23.5)	238	61.4 (22.7)	241	63.6 (23.1)	243	
6 months	51.9 (27.9)	327	25.7 (23.5)	352	31.9 (27.1)	329	
12 months	51.5 (27.4)	333	30.1 (23.2)	352	43.2 (27.6)	346	
24 months	48.2 (27.5)	368	33.3 (23.3)	388	43.4 (25.2)	372	
36 months	45.9 (28.4)	413	33.9 (23.9)	413	42.5 (25.9)	414	
48 months	44.5 (26.9)	432	34.3 (24.2)	444	41.8 (25.5)	443	
60 months	43.2 (27.4)	439	34.5 (24.0)	454	40.1 (24.4)	455	
72 months	40.6 (26.7)	437	32.3 (23.2)	454	41.3 (24.9)	440	<0.001
<b>EPIC sexual function sub-scale score</b>							
Baseline	53.5 (22.8)	241	54.4 (22.9)	240	55.7 (23.0)	245	
6 months	45.1 (27.0)	329	19.9 (22.4)	351	23.2 (27.0)	333	
12 months	44.4 (27.1)	332	23.6 (22.8)	352	36.6 (27.0)	345	
24 months	41.9 (26.7)	367	27.2 (23.4)	387	36.9 (25.1)	377	
36 months	39.2 (27.4)	418	26.9 (23.7)	420	35.7 (25.5)	419	
48 months	37.2 (26.5)	437	27.1 (24.2)	444	34.3 (25.4)	446	
60 months	35.6 (27.3)	447	26.5 (24.4)	457	31.9 (24.8)	463	
72 months	32.5 (26.4)	444	23.7 (23.4)	459	32.7 (25.6)	449	<0.001
<b>EPIC sexual bother sub-scale score</b>							
Baseline	76.0 (30.5)	236	77.6 (28.9)	242	80.5 (29.2)	241	
6 months	66.9 (35.3)	327	38.7 (35.0)	351	51.9 (39.3)	330	
12 months	67.8 (34.3)	335	44.5 (34.1)	353	57.6 (36.5)	345	
24 months	62.2 (35.4)	373	46.8 (33.1)	392	57.9 (33.5)	371	
36 months	60.7 (36.3)	414	49.6 (34.8)	413	57.1 (34.9)	416	
48 months	60.4 (35.8)	433	50.4 (34.2)	443	58.2 (34.7)	446	
60 months	60.1 (36.3)	441	52.6 (35.1)	456	58.9 (35.3)	459	
72 months	57.9 (36.6)	434	51.4 (35.5)	448	60.1 (34.9)	443	<0.001
<b>EPIC: Moderate/severe impact of sexual dysfunction on QoL</b>							
Baseline	44/239	(18.4)	39/245	(15.9)	31/244	(12.7)	
6 months	91/328	(27.7)	226/355	(63.6)	152/334	(45.5)	
12 months	95/335	(28.4)	191/355	(53.8)	135/348	(38.8)	
24 months	129/375	(34.4)	194/395	(49.1)	137/378	(36.2)	
36 months	140/414	(33.8)	188/417	(45.1)	153/418	(36.6)	
48 months	147/436	(33.7)	197/451	(43.7)	157/447	(35.1)	
60 months	154/444	(34.7)	208/462	(45.0)	143/461	(31.0)	
72 months	164/438	(37.4)	190/457	(41.6)	150/448	(33.5)	<0.001

**Table S2C. Bowel function and impact on QoL: Overall bowel function scores**

	AM		RP		RT		p-value
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	
<b>EPIC bowel summary score</b>							
Baseline	92.8 (9.1)	247	93.1 (8.9)	254	94.8 (6.9)	247	
6 months	92.8 (9.1)	348	92.9 (9.0)	363	86.3 (16.0)	345	
12 months	93.4 (8.6)	356	94.0 (7.7)	362	90.5 (12.2)	358	
24 months	93.2 (9.4)	394	93.8 (8.2)	405	89.3 (12.8)	391	
36 months	92.8 (10.8)	433	93.8 (8.0)	436	90.8 (11.2)	430	
48 months	92.9 (11.2)	456	93.7 (8.9)	458	91.2 (11.2)	454	
60 months	93.1 (10.1)	461	94.0 (7.9)	469	91.0 (10.6)	473	
72 months	93.0 (9.8)	457	93.2 (8.7)	463	91.2 (10.9)	466	<0.001
<b>EPIC bowel function sub-scale score</b>							
Baseline	91.6 (9.0)	249	91.4 (9.3)	254	92.9 (8.0)	249	
6 months	91.4 (9.8)	348	91.7 (8.8)	363	86.3 (14.9)	347	
12 months	92.1 (8.6)	357	92.8 (8.1)	363	90.3 (11.1)	358	
24 months	92.2 (19.1)	395	92.6 (8.5)	406	89.5 (10.7)	391	
36 months	91.9 (10.0)	435	92.7 (8.1)	437	90.7 (10.1)	432	
48 months	92.2 (10.8)	459	93.0 (8.4)	458	90.7 (10.1)	458	
60 months	92.0 (9.5)	461	92.9 (7.7)	469	90.3 (10.1)	473	
72 months	92.3 (9.7)	461	92.3 (8.6)	463	90.8 (9.7)	466	<0.001
<b>EPIC bowel bother sub-scale score</b>							
Baseline	94.0 (11.8)	248	94.7 (10.3)	256	96.8 (7.1)	247	
6 months	94.2 (10.6)	348	94.0 (10.7)	363	86.4 (18.7)	345	
12 months	94.7 (10.4)	356	95.2 (9.1)	363	90.7 (14.9)	359	
24 months	94.2 (11.7)	394	95.0 (9.4)	405	89.2 (16.7)	395	
36 months	93.7 (13.1)	437	94.9 (9.8)	439	90.9 (14.3)	431	
48 months	93.8 (12.7)	459	94.6 (11.1)	459	91.7 (13.8)	456	
60 months	94.1 (12.2)	470	95.1 (9.6)	473	91.6 (13.2)	480	
72 months	93.7 (11.6)	460	94.2 (10.8)	465	91.7 (13.7)	472	<0.001

**Table S2C continued. Bowel function and impact on quality of life: Bowel function items**

	AM		RP		RT		p-value
	n / N	(%)	n / N	(%)	n / N	(%)	
<b>EPIC: Fecal incontinence more than once per week</b>							
Baseline	5/249	(2.0)	7/255	(2.8)	1/250	(0.4)	
6 months	6/348	(1.7)	4/367	(1.1)	18/346	(5.2)	
12 months	4/356	(1.1)	3/363	(0.8)	14/358	(3.9)	
24 months	10/395	(2.5)	8/406	(2.0)	17/393	(4.3)	
36 months	10/436	(2.3)	8/437	(1.8)	11/433	(2.5)	
48 months	12/460	(2.6)	8/459	(1.7)	11/458	(2.4)	
60 months	11/463	(2.4)	6/472	(1.3)	11/476	(2.3)	
72 months	12/462	(2.6)	9/468	(1.9)	19/465	(4.1)	0.027
<b>EPIC: Loose stools about half the time or more frequently</b>							
Baseline	43/249	(17.3)	36/255	(14.2)	39/250	(15.6)	
6 months	68/348	(19.5)	51/366	(13.9)	87/347	(25.1)	
12 months	57/357	(16.0)	45/363	(12.4)	77/358	(21.5)	
24 months	56/396	(14.1)	57/406	(14.0)	77/392	(19.6)	
36 months	65/436	(14.9)	50/435	(11.5)	68/433	(15.7)	
48 months	68/461	(14.8)	46/460	(10.0)	73/459	(15.9)	
60 months	66/465	(14.2)	57/473	(12.1)	85/475	(17.9)	
72 months	61/466	(13.1)	57/468	(12.2)	72/466	(15.5)	<0.001
<b>EPIC: Bloody stools about half the time or more frequently</b>							
Baseline	5/247	(2.0)	3/255	(1.2)	4/250	(1.6)	
6 months	7/348	(2.0)	1/363	(0.3)	13/347	(3.8)	
12 months	5/357	(1.4)	2/364	(0.6)	14/357	(3.9)	
24 months	3/396	(0.8)	1/407	(0.3)	29/392	(7.4)	
36 months	7/435	(1.6)	5/436	(1.2)	32/433	(7.4)	
48 months	10/460	(2.2)	4/459	(0.9)	34/459	(7.4)	
60 months	10/465	(2.2)	4/471	(0.9)	40/476	(8.4)	
72 months	6/465	(1.3)	5/470	(1.1)	26/466	(5.6)	<0.001

**Table S2C continued: Bowel function and impact on quality of life**

	AM		RP		RT		p-value
	n / N	(%)	n / N	(%)	n / N	(%)	
<b>EPIC: Moderate/severe impact of bowel habits on quality of life</b>							
Baseline	11/249	(4.4)	5/255	(2.0)	4/247	(1.6)	
6 months	11/348	(3.2)	12/362	(3.3)	36/345	(10.4)	
12 months	6/358	(1.7)	9/364	(2.5)	21/359	(5.9)	
24 months	10/395	(2.5)	6/407	(1.5)	25/395	(6.3)	
36 months	11/439	(2.5)	9/439	(2.1)	20/432	(4.6)	
48 months	14/461	(3.0)	10/459	(2.2)	14/458	(3.1)	
60 months	16/471	(3.4)	11/473	(2.3)	18/480	(3.8)	
72 months	16/463	(3.5)	12/467	(2.6)	10/472	(2.1)	0.003

**Table S2D. Health-related quality of life: Generic health status scores**

	AM		RP		RT		p-value
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	
<b>SF-12: Physical health sub-scale</b>							
Baseline	49.9 (8.9)	514	51.0 (8.1)	512	51.0 (7.7)	507	
6 months	50.0 (8.7)	430	47.4 (9.7)	443	48.7 (8.8)	437	
12 months	49.9 (9.1)	453	49.9 (8.5)	447	50.2 (8.6)	440	
24 months	49.5 (9.1)	444	50.4 (8.3)	437	49.9 (8.9)	438	
36 months	48.5 (9.8)	444	49.4 (8.7)	440	49.7 (8.9)	438	
48 months	48.7 (9.3)	446	49.1 (8.7)	440	48.9 (9.4)	441	
60 months	48.3 (9.4)	440	48.6 (9.2)	429	48.1 (9.7)	437	
72 months	46.9 (10.6)	428	48.8 (9.1)	428	48.4 (9.4)	428	0.65
<b>SF-12: Mental health sub-scale</b>							
Baseline	53.3 (8.1)	514	53.7 (8.0)	512	54.1 (6.8)	507	
6 months	53.1 (8.6)	430	52.5 (9.1)	443	52.2 (8.7)	437	
12 months	53.6 (8.1)	453	53.7 (8.3)	447	53.3 (8.5)	440	
24 months	53.3 (8.3)	444	53.5 (8.6)	437	52.9 (8.5)	438	
36 months	53.1 (8.5)	444	53.8 (8.3)	440	53.9 (7.9)	438	
48 months	53.6 (8.4)	446	54.3 (7.9)	440	53.8 (8.0)	441	
60 months	52.9 (8.9)	440	53.8 (7.9)	429	53.8 (8.1)	437	
72 months	53.0 (8.8)	428	53.5 (8.3)	428	53.8 (7.8)	428	0.47



**Table S2D continued. Health-related quality of life: Hospital Anxiety and Depression Scale (HADS) scores**

	AM		RP		RT		p-value
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	
<b>HADS: Anxiety sub-scale scores</b>							
Baseline	5.1 (3.6)	529	5.0 (3.5)	539	4.6 (3.3)	523	
6 months	3.9 (3.7)	467	4.0 (3.6)	485	4.0 (3.6)	476	
12 months	4.0 (3.6)	479	3.6 (3.6)	472	3.7 (3.6)	471	
24 months	3.9 (3.6)	467	3.6 (3.4)	474	3.7 (3.4)	470	
36 months	3.9 (3.8)	474	3.7 (3.4)	470	3.7 (3.5)	466	
48 months	4.0 (3.9)	475	3.8 (3.5)	471	3.6 (3.3)	473	
60 months	3.8 (3.7)	464	3.6 (3.2)	470	3.6 (3.4)	479	
72 months	4.1 (3.9)	458	3.7 (3.5)	465	3.4 (3.2)	465	0.20
<b>HADS: Depression sub-scale scores</b>							
Baseline	2.7 (2.7)	530	2.5 (2.5)	539	2.4 (2.5)	524	
6 months	2.4 (3.0)	470	2.8 (3.0)	487	2.7 (3.0)	478	
12 months	2.4 (2.8)	481	2.4 (2.9)	475	2.5 (2.7)	470	
24 months	2.6 (3.0)	472	2.5 (2.7)	480	2.6 (2.9)	471	
36 months	2.7 (3.2)	476	2.5 (2.8)	471	2.7 (3.0)	467	
48 months	2.7 (3.1)	476	2.6 (3.0)	471	2.7 (3.0)	476	
60 months	2.8 (3.1)	466	2.6 (2.9)	471	2.7 (3.0)	480	
72 months	3.1 (3.4)	464	2.7 (3.1)	459	2.7 (2.9)	464	0.85

**Table S2D continued. Health-related quality of life: Hospital Anxiety and Depression Scale (HADS) cases**

	AM		RP		RT		p-value
	n / N	(%)	n / N	(%)	n / N	(%)	
<b>HADS: Anxiety possible case scoring 8+</b>							
Baseline	120/529	(22.7)	107/539	(19.9)	93/523	(17.8)	
6 months	75/467	(16.1)	71/485	(14.6)	74/476	(15.6)	
12 months	84/479	(17.5)	61/472	(12.9)	62/471	(13.2)	
24 months	70/467	(15.0)	58/474	(12.2)	61/470	(13.0)	
36 months	76/474	(16.0)	56/470	(11.9)	68/466	(14.6)	
48 months	68/475	(14.3)	65/471	(13.8)	62/473	(13.1)	
60 months	75/464	(16.2)	55/470	(11.7)	67/479	(14.0)	
72 months	69/458	(15.1)	69/465	(14.8)	53/465	(11.4)	0.27
<b>HADS: Depression possible case scoring 8+</b>							
Baseline	41/530	(7.7)	32/539	(5.9)	26/524	(5.0)	
6 months	31/470	(6.6)	37/487	(7.6)	37/478	(7.7)	
12 months	27/481	(5.6)	36/475	(7.6)	32/470	(6.8)	
24 months	33/472	(7.0)	34/480	(7.1)	33/471	(7.0)	
36 months	35/476	(7.4)	30/471	(6.4)	38/467	(8.1)	
48 months	38/476	(8.0)	43/471	(9.1)	40/476	(8.4)	
60 months	42/466	(9.0)	38/471	(8.1)	44/480	(9.2)	
72 months	47/464	(10.1)	43/459	(9.4)	35/464	(7.5)	0.96

**Table S2D continued. Cancer-specific quality of life: EORTC-QLQ-C30 at 5 years**

	AM		RP		RT		p-value
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	
Global health status	76.8 (17.6)	394	78.4 (17.7)	386	77.4 (19.0)	400	0.38
<b>Functional scales</b>							
Physical	90.9 (14.7)	395	91.6 (13.8)	383	91.3 (14.1)	396	0.81
Role	90.5 (19.7)	395	90.9 (19.0)	383	89.5 (20.1)	396	0.60
Emotional	87.3 (17.3)	394	87.9 (16.0)	386	87.7 (16.6)	398	0.79
Cognitive	86.0 (15.4)	394	87.9 (14.4)	386	87.3 (15.7)	399	0.21
Social	91.3 (17.2)	394	91.3 (16.8)	386	91.6 (17.8)	399	0.95
<b>Symptom scales and items</b>							
Fatigue	19.0 (19.4)	395	17.1 (17.9)	383	17.3 (17.1)	395	0.24
Nausea and vomiting	2.0 (7.1)	395	1.4 (6.2)	383	1.7 (5.9)	397	0.44
Pain	12.0 (20.5)	396	9.7 (18.1)	386	11.9 (20.2)	400	0.20
Dyspnoea	12.4 (22.1)	394	10.1 (20.0)	383	11.3 (19.9)	397	0.34
Insomnia	18.3 (25.6)	393	14.6 (22.4)	383	16.0 (23.1)	396	0.08
Appetite loss	4.9 (13.6)	395	3.8 (11.9)	383	4.2 (13.2)	397	0.56
Constipation	6.4 (15.7)	394	4.6 (14.3)	381	5.1 (14.0)	396	0.25
Diarrhoea	6.0 (15.3)	390	6.0 (16.4)	384	5.6 (13.7)	400	0.89
Financial difficulties	3.1 (13.8)	394	3.4 (12.7)	383	2.8 (11.9)	398	0.80

### **Section S3:**

## **Some factors relating to the design and analysis of the ProtecT trial and its treatment policies that could affect patient-reported outcome measure scores**

Several factors related to the design and analysis of the ProtecT trial and its treatment policies may have influenced some overall patient-reported outcome scores. These factors include:

#### *(a) The timing of receipt of radical treatment*

The immediate receipt of prostatectomy by 68% and radiotherapy by 73% in these arms (Table S3A below) will probably have attenuated some scores, and in the active monitoring arm, the increasing numbers of men receiving radical treatments will have conflated outcomes, contributing to the gradual worsening of scores. Table S3B below shows that men remaining on active monitoring had lower pad-use and less erectile dysfunction than those in the full allocated active monitoring arm - although this exploratory subgroup analysis requires cautious interpretation.

#### *(b) Receipt of neo-adjuvant androgen deprivation with radiotherapy*

The assessment of patient-reported outcomes at six months post-randomization will have captured the impact of neo-adjuvant androgen suppression on sexual function in the radiotherapy arm.

#### *(c) The effects of therapies to ameliorate the side-effects of treatments.*

The ProtecT trial was designed as a pragmatic study carried out in nine centers within the UK and so treatment pathways were outlined in the trial protocol to reflect best practice in the NHS with all centers following established clinical guidelines for clinical care. Guidelines include those produced by NICE (UK National Institute for Health and Care Excellence) and EAU (European Association of Urology) specifically for therapies to ameliorate the side effects of the study interventions, as well as the similar AUA (American Urology Association) guidelines for treatment of erectile dysfunction. In relation to specific treatments, for urinary incontinence, these included lifestyle advice, containment interventions, behavioral and physical interventions, pharmacological interventions or surgery, depending on severity. For erectile dysfunction, these included pharmacological interventions, intracavernous injections, combination therapies and prostheses, depending on severity. For radiation-induced symptoms, specialist care was sought. The results in this paper represent patient reporting of the overall effect of randomly allocated treatments and ameliorating therapies. Analyses to separate out effects of interventions from concomitant therapies are complex, and the interpretation of the resulting estimates difficult.

#### **Future analyses**

In future analyses, we intend to present patient-reported outcomes according to treatment received and an economic evaluation including assessment of therapies received for treatment impacts, as well as details about the reasons for change of management in the active monitoring arm to further inform individual and clinical decision-making.

**Table S3A Prostatectomy and radical radiotherapy received in each trial arm over time**

	Allocated to active monitoring (n=545)		Allocated to prostatectomy (n=553)		Allocated to radiotherapy (n=545)	
	Prostatectomy received	Radiotherapy received	Prostatectomy received	Radiotherapy received	Prostatectomy received	Radiotherapy received
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
6 months	41 (7.5)	18 (3.3)	373 (67.5)	30 (5.4)	38 (7.0)	392 (71.9)
12 months	49 (9.0)	24 (4.4)	399 (72.2)	35 (6.3)	42 (7.7)	402 (73.8)
24 months	65 (11.9)	32 (5.9)	403 (72.9)	38 (6.9)	47 (8.6)	409 (75.1)
36 months	81 (14.9)	42 (7.7)	408 (73.8)	38 (6.9)	49 (9.0)	409 (75.1)
48 months	97 (17.8)	50 (9.2)	411 (74.3)	40 (7.2)	53 (9.7)	411 (75.4)
60 months	112 (20.6)	60 (11.0)	416 (75.2)	44 (8.0)	54 (9.9)	412 (75.6)
72 months	121 (22.2)	71 (13.0)	417 (75.4)	46 (8.3)	55 (10.1)	414 (76.0)

**Table S3B. Tabular presentation of selected EPIC outcomes for urinary incontinence and erectile dysfunction, comparing the active monitoring group with those who were not radically treated within six years of randomization**

	Whole group		No radical treatment	
	n / N	(%)	n / N	(%)
<b>One or more pads per day in past 4 weeks (EPIC item)</b>				
Baseline	1/250	(0.4)	0/132	(0.0)
6 months	15/346	(4.3)	0/186	(0.0)
12 months	15/357	(4.2)	0/191	(0.0)
24 months	15/392	(3.8)	1/210	(0.5)
36 months	22/434	(5.1)	1/241	(0.4)
48 months	31/455	(6.8)	4/258	(1.6)
60 months	32/461	(6.9)	4/265	(1.5)
72 months	38/453	(8.4)	5/266	(1.9)
<b>EPIC: Erections firm enough for intercourse</b>				
Baseline	164/243	(67.5)	81/125	(64.8)
6 months	173/375	(51.6)	102/179	(57.0)
12 months	167/340	(49.1)	97/182	(53.3)
24 months	178/378	(47.1)	104/204	(51.0)
36 months	173/421	(41.1)	119/235	(50.6)
48 months	163/442	(36.9)	121/256	(47.3)
60 months	157/449	(35.0)	114/255	(44.7)
72 months	134/452	(29.6)	99/263	(37.6)