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Bristol Randomised Trials Collaboration

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Bristol Randomised Trials Collaboration (BRTC)

Prostate Testing for Cancer and Treatment (ProtecT) Study

Statistical Analysis Plan

Version 1.0 (19th November 2015)

The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents			
Name	**Role**	**Signature**	**Date**
Chris Metcalfe	Author	Chris Metcalfe	19/11/2015
Tim Peters	Statistical Reviewer	T. J. Peters	19.11.15
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1. INTRODUCTION & PURPOSE

This document details the statistical analysis proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from the **Prostate Testing for Cancer and Treatment (ProtecT) Study**.

The core of this statistical analysis plan is unchanged from that laid out in the protocol (Version 1.0, September 2001), with subsequent changes due to clarifications and further detail. Hence the key decisions had been made and documented prior to unblinded analyses being conducted in confidence for the Data Monitoring Committee.

The purpose of the plan is to:

1. Make explicit the details of the planned analysis, as agreed with the Trial Steering Committee.

2. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of *a priori* and post-hoc analyses is appropriate.

3. Explain in detail how the data will be handled and analysed to enable others to perform the actual analysis in the event of sickness or other absence, or to replicate the analyses

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan (although such analyses would be expected to follow Good Statistical Practice).

The analysis strategy will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with the Analysis Plan, but if reported the source of such a post-hoc analysis will be declared.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial.

2. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

IMPORTANT: *This synopsis is purely to provide background information for those reading the statistical analysis plan. It does not replace the study protocol; the current version of which must be consulted for all other purposes.*

2.1. Trial objectives and aims

The ProtecT trial was designed in the late 1990s and early 2000s to compare the major conventional treatments for patients with clinically localised prostate cancer detected through population-based PSA testing. The three treatments were radical prostatectomy, external beam three-dimensional (3D) conformal radiotherapy, and active monitoring.

2.1.1. Primary objective

In men with localised prostate cancer detected through population-based PSA testing, to compare definite or probable prostate cancer specific mortality (including definite or probable intervention related mortality) at a median of 10 years following random allocation to radical prostatectomy, external beam three dimensional (3D) conformal radiotherapy, and active monitoring.

2.1.2. Secondary objectives

To make the same comparison on a number of secondary outcome measures, including overall survival, clinical disease progression, treatment complications, lower urinary tract symptoms, quality of life, and sexual function. To estimate the resource use and costs of case-finding, treatment and follow-up, and to compare costs and outcomes of treatment in terms of survival and health related quality of life.

2.2. Trial design and configuration

A three parallel groups randomised controlled trial.

2.3. Trial centres

Recruitment to the trial took place at general practices in and around nine study centres across the UK: Newcastle, Sheffield, Bristol, Cardiff, Edinburgh, Birmingham, Leicester, Cambridge, and Leeds.

2.4. Eligibility criteria

2.4.1. Inclusion criteria

- Men
- Age 50-69 years on the date of preparation at the general practice of the list of potential participants
- Able to give written informed consent to participate
- Fit for any of the three treatments and with a life expectancy of at least 10 years
- Registration with the participating general practice on the date of the PCC
- For randomisation: clinically localized prostate cancer (confirmed by isotope bone scan in men with PSA of 10ng/L or more) diagnosed by 10-core biopsy following a PSA level of 3ng/L or more.

2.4.2. Exclusion criteria

- Concomitant or past malignancies (other than a small treated skin cancer)
- Prior treatment for prostate malignancy
- Serious cardiac or respiratory problems in the previous 12 months of the PCC, e.g. stroke, MI, heart failure, COPD
- Kidney dialyses or transplantation
- Bilateral hip replacement
- Previous entry to the ProtecT study at a prior general practice
- PSA 20ng/L or more at diagnosis

2.5. Description of interventions

The **Active Monitoring Protocol** aimed to avoid immediate radical treatment whilst assessing the disease over time, with a review and the opportunity for radical treatment if there was evidence of disease progression. PSA levels were measured and reviewed every three months in the first year and twice yearly thereafter. Changes in PSA levels were assessed, and a rise of at least 50% over the previous 12 months triggered repeat testing within six to nine weeks. If the PSA levels were persistently raised, or the patient had other concerns, a review appointment was made to consider treatment options.

The **Radiotherapy Protocol** began with neoadjuvant androgen suppression, given for three to six months before and concomitantly with 3D-conformal radiation therapy delivered at 74 Gy in 37 fractions.

Surgery was a radical retropubic prostatectomy procedure. The surgical approach was left to the discretion of the surgeon, and was most commonly open, but laparoscopic, or robot-assisted approaches were permitted from 2003.

2.6. Randomisation procedures

Once a man agreed to have his treatment determined by random allocation, the research nurse telephoned a central system for a computer-generated allocation. Randomisation was stratified by centre with stochastic minimization by age at invitation, Gleason score (primary and secondary grades), and mean of baseline and first biopsy PSA results. Men who declined randomisation were offered identical follow-up, and formed an observational patient preference cohort.

2.7. Sample size and justification

Following a review of the likely disease-specific mortality with active monitoring, the Data Monitoring Committee advised in 2008 that recruitment should continue to a projected target of 1590 (530 per arm). This would enable a risk ratio of 0.54 to be detected with 80% power at the 5% significance level for a pairwise comparison of each radical treatment with active monitoring. This assumes 10% prostate cancer specific mortality at 10 years in men managed with active monitoring, equivalent to an absolute difference of 10% versus 5.4%.

2.8. Blinding

A panel of clinicians, otherwise independent of the study, confirmed cause of death for those deaths known to be at risk of miscoding in death certificates from previous trials of prostate cancer detection (ERSPC) and treatment (SPCG-4). These clinicians were kept blind to each man's treatment allocation, by having the clinician consider information in a vignette extracted from a man's medical record rather than consulting the record directly.

2.9. Trial committees

ProtecT has a Trial Steering Committee, chaired by Professor Michael Baum (University College London). Reporting to that committee is an Independent Data Monitoring Committee, chaired by Professor Adrian Grant (University of Aberdeen) until 2012 and subsequently by Professor Ian Roberts (London School of Hygiene and Tropical Medicine).

2.10. Outcome measures

2.10.1. Primary outcome

The primary outcome is definite or probable prostate cancer mortality, including intervention-related deaths, at a median 10 years' follow-up.

The process used to assess cause of death was adapted from the PLCO algorithm and ERSPC process. The medical records of deceased participants were summarised by trained researchers, anonymised and reviewed by an independent endpoint committee. Table 2 presents the classification of deaths by study arm.

2.10.2. Secondary outcomes

Secondary clinical, economic and patient-reported outcomes to be presented in the primary results papers are:

- overall mortality
- metastatic disease
- primary treatment failure:
    - for radical prostatectomy: PSA 0.2ng/ml+ at three months post-surgery
    - for the radiotherapy protocol: according to the ASTRO criteria (Roach, 2006).
- clinical disease progression
- treatment complications
- resource use (the subject of a separate economic analysis plan)

Metastatic disease is defined as positive imaging showing bony, visceral and/or lymph node metastases, or PSA above 100; or bone marrow infiltration with associated systemic symptoms.

Clinical disease progression will be measured as person-years free of the consequences of disease progression. Signs of disease progression will include evidence of metastatic disease; the initiation of hormone therapy; diagnosis of clinical T3 or T4 disease; or ureteric obstruction, rectal fistula, or the need for a permanent catheter when these are not considered to be a complication of treatment.

The *treatment complications* listed in Table A will be recorded, following the indicated interventions. Complications following radical therapy will be presented irrespective of whether the man was allocated to that intervention, chose it following allocation, or it was recommended after a period of active monitoring.

The patient-reported outcomes which have been measured are listed in the Appendix. These measures are derived from validated questionnaires and have

been completed at recruitment, at first biopsy, six months after randomisation, and yearly thereafter for at least 10 years. These measures will be reported in a separate companion paper, to be submitted for publication at the same time as the primary outcomes paper.

Table A. Serious intervention-related complications occurring between intervention initiation and 90 days after intervention completion, which will be reported following the indicated interventions

	Active monitoring protocol*	Surgery	Radiotherapy protocol
Death	X	X	X
Hospital admission lasting more than 10 days	X	X	
Hospital admission for sepsis	X	X	X
Hospital readmission	X	X	X
Rectal, bowel or bladder injury or damage		X	X
Ureteric injury or damage		X	X
Urethral or anastomotic problem requiring intervention		X	X
More than three units of blood transfused		X	
Thromboembolic-cardiovascular event		X	

*Following a repeat biopsy, for example.

2.11. Interim analysis

A confidential interim analysis, by study arm, of primary and secondary outcomes has been presented to the annual meeting of the Data Monitoring Committee since 2004. The Data Monitoring Committee recommends changes to the Trial Steering Committee if clear evidence (of the order of $p<0.001$) of a positive or negative balance of risks and benefits emerges for one intervention in comparison with the others.

3. GENERAL ANALYSIS CONSIDERATIONS

3.1. Analysis populations

The primary analysis data set is all men randomised to one of the three management options being compared in the ProtecT trial.

3.2. Procedures for missing data

There are no missing data for the minimisation variables. Men are linked for vital status notification with the NHS national registry, ensuring almost all primary

outcome events are captured. When we are notified that a man has emigrated, the man's inclusion in the analysis will be censored on the date of emigration. The number of men emigrating will be presented, broken down by random allocation.

Where a man has omitted responding to a small number of items on a patient reported outcome measure, these will be imputed as per the guidance for that measure. However, where the patient has not responded to any or most of the items on a measure, the main analysis of patient-reported outcomes will NOT be based on data with those missing scale scores imputed. However, the amount of missing data, by allocation arm, will be presented. All men providing at least one post-randomisation patient-reported measure will be included in the relevant analysis.

3.3. Study centre effects

The primary analysis will be stratified by study centre, by using dummy variables in the regression equation to distinguish the nine study centres. For the main trial paper there is no plan to investigate whether estimated treatment effects vary by study centre.

3.4 Acceptance of allocated intervention

With regard to the surgery and radiotherapy protocols, a participant is considered to have accepted their allocated intervention if he has commenced that treatment (in any way) within nine months of randomisation. Similarly, a participant is considered to have accepted the active monitoring protocol if he has undergone at least one PSA test for monitoring within nine months of randomisation and not undergone radical treatment in that time.

4. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

4.1. Disposition

Details of the recruitment of the ProtecT randomised trial cohort, up to the point of randomisation, were presented in the *Baseline Paper* (Lane et al, 2014). Details of how many men were excluded and for what reasons are presented. The subsequent flow of patients through the trial will be summarised in a CONSORT diagram that will include the numbers randomised to the three treatment groups, losses to follow-up and the numbers analysed (Figure 1).

4.2. Baseline characteristics

These are presented as descriptive statistics in the *Baseline Paper* (Lane, 2014).

5. ASSESSMENT OF STUDY QUALITY

5.1. Eligibility checks

The numbers of patients excluded from random allocation of treatment are reported with reasons in the *Baseline Paper* (Lane, 2014).

5.2. Protocol deviations

The first treatment received within nine months of random allocation will be tabulated by allocated treatment, to illustrate the extent of initial non-compliance with randomised allocation (Table 1). Active monitoring commences with the first PSA monitoring test; this does not include PSA tests undertaken whilst waiting for surgery or radiotherapy within eight months of randomisation. Radiotherapy commences with the first fraction.

In addition, the date on which radical treatment is received by those allocated to active monitoring will be recorded. This can be compared with each man's PSA series to identify those changes to radical treatment which did not follow an increase in PSA level, as described in the active monitoring protocol. The cumulative proportion of these who undergo radical treatment over the follow-up period will be plotted against time (Figure 2).

Treatments received by men in each treatment allocation arm following any changes within three years and five years of randomisation will be reported.

6. ANALYSIS OF EFFECTIVENESS

6.1. Summary of primary and secondary outcomes

The following summaries of the primary outcome events will be presented for each treatment allocation arm:

- Number of deaths due to prostate cancer (Table 3).
- Prostate cancer mortality at 5 and 10 years, with 95% confidence interval (Table 3).
- Prostate cancer mortality per 1,000 person years of follow-up, with 95% confidence interval (Table 3).
- Cumulative hazards of death from prostate cancer as a function over time (Figure 3).

The following summaries will be presented for the secondary outcome events (Table 4):

- Number of events.
- Events per 1000 person years of follow-up, with 95% confidence interval.

6.2. Primary analysis

The primary analysis will be conducted on an intention-to-treat basis comparing treatment groups as allocated. Deaths occurring until a median of 10-year follow-up has accumulated (midnight 00:00 on Monday 23rd November 2015) will be included in the locked database.

The primary outcome measure of prostate cancer (definite, probable, or intervention-related) mortality will be compared between the three treatment groups using Cox's proportional hazards regression adjusted for study centre (all nine centres distinguished using dummy variables), age at baseline (continuous measure in years), Gleason score (2-6, 7, 8-10), and PSA at baseline (continuous measure in ng/ml, log-transformed to accommodate positive skewed distribution):

$$h(t) = h_0(t)\exp\{\beta_{1j}x_{1i} + \beta_{2k}x_{2i} + \beta_3 x_{3i} + \beta_{4m}x_{4i} + \beta_5 ln.x_{5i}\}$$

β_{1j} is the log hazard ratio comparing two of the treatment arms, with two of the three pairwise comparisons being available from a single iteration of the analysis (i.e. j=1,2 the estimated comparisons depending on the choice of comparator treatment). x_{1i} is the treatment allocation (0,1,2) for participant i. β_{2k} (k=1 to 8) captures differences in the hazard of the primary outcome event between study centres, x_{2i} being the study centre for participant i. β_3 is the linear effect of age, with x_{3i} being the age in years for participant i. β_{4m} (m=1,2) accommodates the effect of Gleason score category with x_{4i} being the Gleason score category for participant i. Finally β_5 is the linear effect of log-transformed PSA level, x_{5i} being the PSA level at diagnosis for participant i.

The hazard ratio and 95% confidence interval for the treatment effect estimated in each pairwise comparison of allocated treatments will be presented, but pairwise significance tests will only be conducted if a test of an equal 10-year disease specific mortality risk across all three arms yields a p-value of less than 0.05 (Table 3). This conditional approach keeps the overall false positive rate at 5%, and has been found to maintain power in simulation studies (Bauer 1991).

6.3. Secondary analyses

The approach to the primary analysis will be adapted to the analysis of secondary outcome events, i.e. definite, probable or possible prostate cancer mortality; all-cause mortality; and metastatic cancer (Table 4).

Patient reported outcomes (see Section 2.10.2) by allocated groups (i.e. following the ITT principle) will be presented in a separate companion paper. Summary statistics by group will be presented graphically for the baseline, 6 month, 12 month and subsequent assessment points. Analyses will employ multi-level models for repeated measures to estimate average treatment effects. Random intercepts and random slopes models will be considered. These analyses will be adjusted for the stratification (centre) and minimisation (baseline age, Gleason score, PSA level) variables as described in the previous section, and the baseline measure of the patient reported outcome being considered. The exact nature of formal testing of differences between groups depends upon the trends observed over time in each; in selecting an analysis, the principles of the primary analysis will be followed as closely as possible, and the most parsimonious set of parameters chosen to describe the differences between groups over time.

6.4. Subgroup analyses

Pre-specified subgroup analyses will investigate whether treatment effectiveness in reducing prostate cancer specific mortality is modified by factors measured at randomisation:

- age (above versus below 65 years)
- clinical stage (T1 v T2)
- Gleason score (score 6 v 7+)
- PSA at diagnosis (PSA < 10ng/ml v 10 and above)

The statistical models used in the primary analysis will be extended to incorporate interaction terms, to test null hypotheses of no variation in treatment effect across subgroups. For sub-group analyses based on age and PSA, the interaction test will be based on the continuous measure, and departures from the assumption of a linear relationship will be investigated (and accommodated if necessary) by introducing polynomial terms. Significance testing will be conducted with the principles of the primary analysis being followed as closely as possible (Table 5).

6.5. Sensitivity analysis

Sensitivity analyses will repeat the primary analysis, but with the following changes made:

- men recruited during the feasibility study period excluded.
- the outcome will be death definitely, probably **and possibly** due to prostate cancer.

7. OTHER ANALYSES

7.1. Patient preference cohort

The analysis of the primary outcome, of secondary outcome events, and of patient-reported outcomes described above will be applied to data collected from the patient preference cohort. The results of this analysis will be compared to that of the randomised trial data, and any differences highlighted.

7.2. Upgrading and upstaging following radical surgery

Grade and stage, as ascertained at histopathology and following radical prostatectomy will be compared.

7.3. Treatment effects in those able to comply with their allocation

A secondary analysis will estimate the relative efficacy of each treatment amongst individuals who do comply with their original allocated treatment. Such an estimate can be considered as a measure of the treatment's potential if, for example, compliance with treatment can be improved through a reduction in the risk of side-effects. Per protocol and on-treatment methods attempt to measure efficacy, but both are almost inevitably biased. Instead we will obtain unbiased estimates of efficacy amongst compliers using complier average causal effect (CACE) methods, extended to the analysis of survival data (Hampson, 2012).

8. FINAL REPORT TABLES AND FIGURES

Figure 1. CONSORT flowchart, illustrating the flow of participants through each of the three arms of the trial, from the point of randomisation. *As per study protocol.

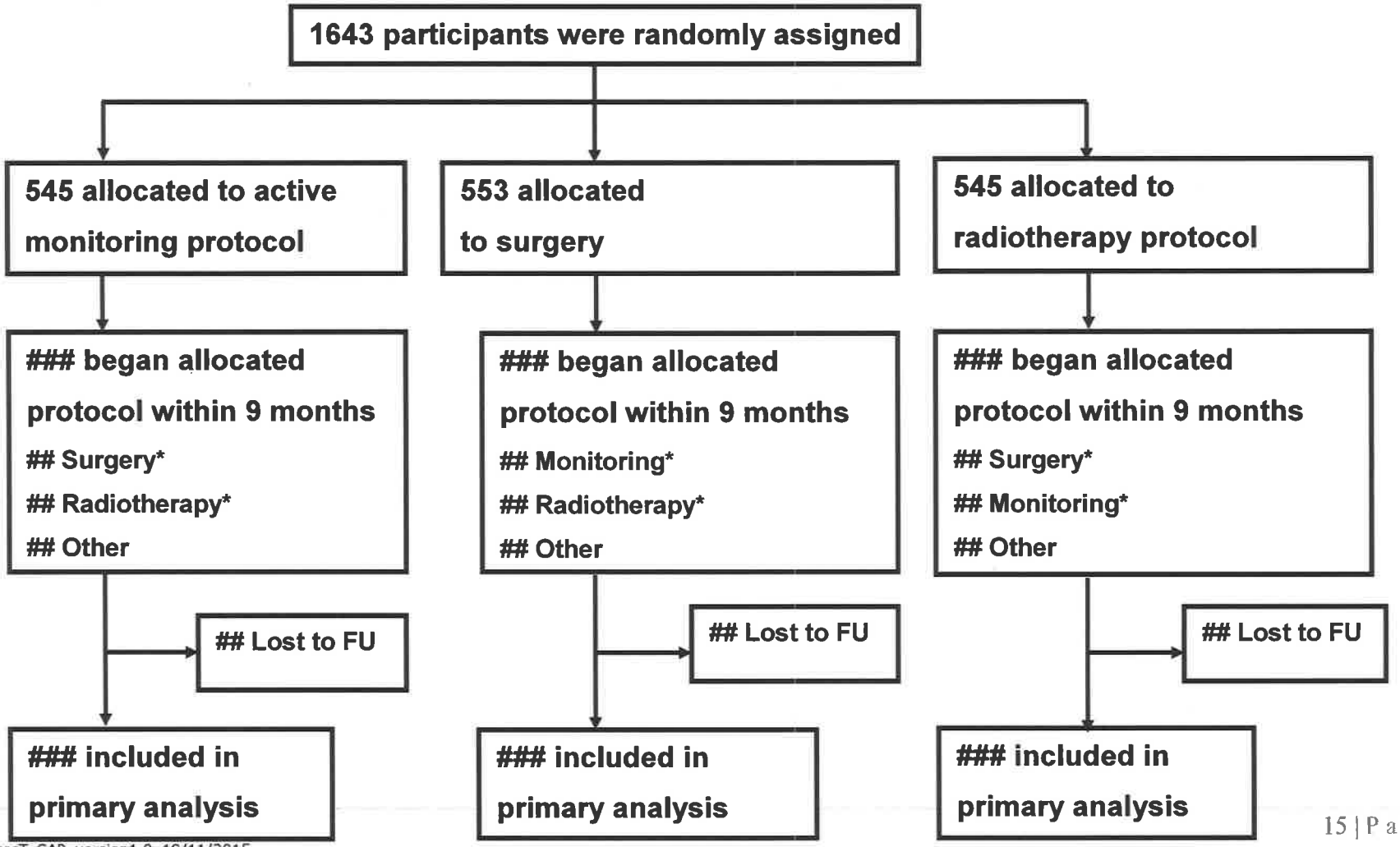

Figure 2. Cumulative probability of being treated radically, for the active monitoring protocol group. The shaded area indicates the proportion of patients who, having followed the active monitoring protocol, changed to the surgery or the radiotherapy study protocol, and the unshaded area non-protocol changes to radical therapy

Figure 3. Cumulative hazards of death from prostate cancer[1] in the active monitoring (solid line), surgery (long dash line) and radiotherapy (short dash line) treatment groups

1. Definitely or probably due to prostate cancer or its treatment, as established by the Independent Cause of Death Evaluation Committee

Figure 4. Cumulative proportion of men over the follow-up period with clinical progression, including metastasis and death due to prostate cancer or its treatment, by randomised treatment group

Table 1. Treatments initiated post-randomisation by random treatment allocation

	Active Monitoring protocol (n=545)	Surgery (n=553)	Radiotherapy protocol (n=545)
First treatment initiated within nine months of randomisation, n (%)			
Active monitoring protocol			
Radical prostatectomy			
Radical radiotherapy protocol			
Other radiotherapy regime			
Other treatment			
No treatment initiated within nine months of randomisation			

Table 2. Likelihood death due to prostate cancer, or treatment of prostate cancer, as established by the independent Cause of Death Evaluation Committee, by randomised treatment group

Cause of death	Active monitoring protocol (N=545)	Surgery (N=553)	Radiotherapy protocol (N=545)
Definite prostate cancer			
Probable prostate cancer			
Possible prostate cancer			
All cause death			

Table 3. Prostate cancer mortality by random allocation

	Active monitoring protocol (N=545)	Surgery (N=553)	Radiotherapy protocol (N=545)	p-value[2]
Total person years in follow-up				
Number of deaths due to prostate cancer[1]				
Percent prostate cancer mortality[1] at 5 years (95% CI)				
Percent prostate cancer mortality[1] at 10 years (95% CI)				
Prostate cancer deaths[1] per 1000 person years (95% CI)				

CI denotes confidence interval

1. Definitely or probably due to prostate cancer or its treatment, as established by the Independent Cause of Death Evaluation Committee
2. Likelihood ratio test of the null hypothesis "no difference in prostate cancer mortality between the three treatment arms", adjusted for study centre, age, mean PSA at prostate check clinic and biopsy, and Gleason score at baseline.

Table 4. Clinical progression, metastatic disease and all-cause mortality, by randomised allocation

	Active monitoring protocol (N=545)	Surgery (N=553)	Radiotherapy protocol (N=545)	p-value[1]
Person years of follow-up free of clinical progression[2]				
Number of men with clinical progression				
Clinical progression per 1000 person years (95% CI)				
Person years of follow-up free of metastatic disease				
Number of men with metastatic disease				
Metastatic disease per 1000 person years (95% CI)				
Total person years in follow-up				
Number of deaths due to any cause				
All-cause deaths per 1000 person years (95% CI)				

[1] Likelihood ratio test of the null hypothesis "no difference in prostate cancer mortality between the three treatment arms", adjusted for study centre, age, mean PSA at prostate check clinic and biopsy, and Gleason score at baseline. [2]Signs of disease progression will include evidence of metastatic disease; the initiation of hormone therapy; diagnosis of clinical T3 or T4 disease; or ureteric obstruction, rectal fistula, or the need for a permanent catheter when these are not considered to be a complication of treatment.

Table 5a. Prostate cancer specific mortality[1], stratified by subgroups

	Rate per 1000pyrs	95% Confidence Interval	P-value[2]
AGE: Below 65 years at randomisation			
Active monitoring protocol			
Surgery			
Radiotherapy protocol			
AGE: 65 years or older at randomisation			
Active monitoring protocol			
Surgery			
Radiotherapy protocol			
PSA AT DIAGNOSIS: Less than 10ng/ml			
Active monitoring protocol			
Surgery			
Radiotherapy protocol			
PSA AT DIAGNOSIS: 10ng/ml+			
Active monitoring protocol			
Surgery			
Radiotherapy protocol			

1. Definitely or probably due to prostate cancer or its treatment, as established by the Independent Cause of Death Evaluation Committee. 2. Likelihood ratio interaction test of the null hypothesis, no difference in relative effectiveness of the three treatments between levels of a subgroup

Table 5b. Prostate cancer specific mortality[1], stratified by subgroups

GLEASON SCORE: 6	
Active monitoring protocol	
Surgery	
Radiotherapy protocol	
GLEASON SCORE: 7+	
Active monitoring protocol	
Surgery	
Radiotherapy protocol	
CLINICAL STAGE: T1c	
Active monitoring protocol	
Surgery	
Radiotherapy protocol	
CLINICAL STAGE: T2	
Active monitoring protocol	
Surgery	
Radiotherapy protocol	

1. Definitely or probably due to prostate cancer or its treatment, as established by the Independent Cause of Death Evaluation Committee. 2. Likelihood ratio interaction test of the null hypothesis, no difference in relative effectiveness of the three treatments between levels of a subgroup

9. APPENDIX

The following standard assessment tools have been completed by men participating in the ProtecT study:

- Expanded Prostate Index Composite
- International Consultation on Incontinence Questionnaire (ICIQ)
- International Continence Society urinary function (ICSmaleSF)
- International Continence Society sexual function (ICSsex)
- EORTC QLQ-C30 cancer-specific impacts
- Hospital Anxiety and Depression Scale
- Short Form 12 (SF-12) mental and physical subscales
- EuroQoL-5D (EQ-5D) generic quality of life

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