Metcalfe, C., Sterne, J. A. C., & Martin, R. M. (2021). *Cluster randomised triAl of PSA testing for Prostate cancer (CAP) Study: 15 year Statistical Analysis Plan: Version 1.0 13th January 2021*. https://doi.org/10.17605/OSF.IO/7Y3G6

## University of Bristol - Explore Bristol Research
### General rights

# CAP: Cluster randomised trial of PSA testing for prostate cancer

## Statistical Analysis Plan 2:
### 15-year follow-up

Version 1.0 (13th January 2021)

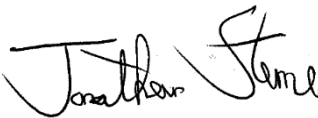| The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents | | | |
|---|---|---|---|
| **Name** | **Role** | **Signature** | **Date** |
| Chris Metcalfe | Author | | 13/01/2021 |
| Jonathan Sterne | Author | | 13/01/2021 |
| Richard Martin | Chief Investigator | | 13/01/2021 |

**Table of Contents**

**Abbreviations**

| CAP | Cluster randomised triAl of testing for Prostate cancer |
|---|---|
| CHD | Coronary heart disease |
| DMC | Data Monitoring Committee |
| ERSPC | European Randomised Study of Screening for Prostate Cancer |
| GP | General Practitioner |
| IMD | Index of multiple deprivation |
| NHS | National Health Service (United Kingdom) |
| NHSCR | National Health Service Central Register (United Kingdom) |
| ONS | Office for National Statistics |
| PHE | Public Health England |
| ProtecT | PROstate TEsting for Cancer and Treatment |
| PSA | Prostate Specific Antigen |
| TNM | Tumour, Nodes, Metastases |
| UK | United Kingdom |

**Trial registration**

ISRCTN Identifier: ISRCTN92187251

## 1. INTRODUCTION & PURPOSE

This document details the statistical analyses that will be undertaken and the presentation that will be followed, as closely as possible, when analysing and reporting **the 15-year median follow-up results** from **the CAP study (Cluster randomised trial of testing for prostate cancer).** Readers are referred to the main statistical analysis plan (Metcalfe et al, 2016) and published papers (Turner et al 2014, Martin et al 2018) for further details of the CAP design, conduct, data, and primary analysis.

The purpose of the plan is to:

1. 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 respectively is appropriate.

2. Explain in detail how the data will be handled and analyzed to enable others to perform the analysis in the event of sickness or other absence

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan. 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

**The information in this section is extracted from the study protocol (Turner et al, 2014) with the single purpose of ensuring an informed statistical analysis. For all other purposes reference MUST be made to the current version of the protocol.**

### 2.1. Trial aims and objectives

To evaluate the effectiveness and cost-effectiveness of population screening for prostate cancer by establishing a cluster randomised trial allocating general practices to either intensive case-finding (the ProtecT trial) or unscreened standard practice.

The objectives are:

1) To provide an unbiased estimate of the effect of a single invitation to screening for prostate cancer on prostate cancer-specific and all-cause mortality in the population.

2) To contribute to the international effort to investigate the impact of prostate cancer screening.

3) To estimate the cost implications of prostate cancer screening and use the data collected to develop and refine a probabilistic model of the cost-effectiveness of prostate cancer screening in the UK.

The primary analysis addressing these objectives has been published (Martin, 2018). These same objectives will be addressed in an analysis of clinical events occurring by the median 15-year follow up point: 31st March 2021.

### 2.2. Trial design and configuration
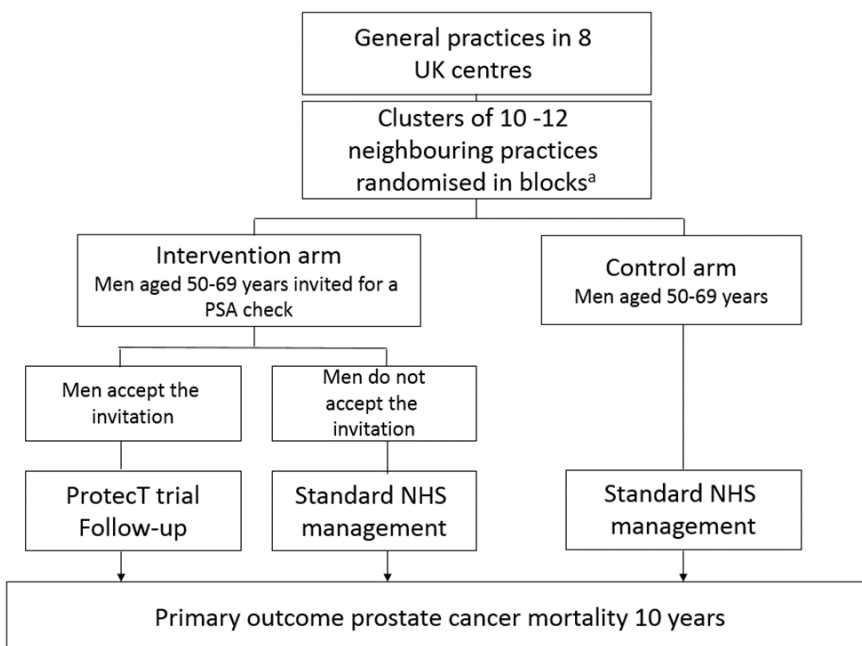


[a]Cluster randomization was blocked and stratified by geographical area.

### 2.3. Trial centres

Sheffield, Newcastle, Bristol, Cardiff, Birmingham, Leicester, Cambridge, Leeds.

### 2.4. Eligibility criteria

### 2.4.1. Inclusion criteria

Men aged 50 to 69 years, registered at a participating GP practice. All GP practices in the study areas were eligible to participate and were included in the random allocation.

### 2.4.2. Exclusion criteria

Men identified as already having a prostate cancer diagnosis on or before the date on which the list of men is generated for a practice. Men excluded by the study consent process (see protocol).

### 2.5. Description of interventions

The intervention was a single invitation to PSA testing at a dedicated prostate cancer check clinic at or near the man's GP practice. Those men found to have a high PSA level were invited to undergo a diagnostic biopsy. Those men found to have clinically localised prostate cancer were invited to have their management randomised in the ProtecT trial of surgery, radiotherapy, and conservative management.

The comparison was standard NHS practice; GPs discussed the risks and potential benefits with those men requesting a PSA test.

### 2.6. Randomisation procedures

The CaP study was cluster randomised. At each study centre, neighbouring groups of eight to twelve GP practices were block-randomised in a 1:1 ratio to PSA testing as part of the ProtecT study, or to NHS usual care in the comparison group. When the group included an odd number of practices, the greater number were allocated to the intervention group. This randomisation was done by an independent statistician (S Brookes) with no other involvement with the study. The randomisation preceded approaches to the GP practices; practices were invited to participate in the group of the study they were allocated to. Allocation was based on random numbers generated using the contemporary version of Stata statistical software (College Station, TX, USA).

### 2.7. Blinding

Members of the cause of death committee see patient vignettes, prepared to obscure the study group the patient is in. Hence decisions about the cause of death are made blind to intervention group (Williams et al, 2015).

### 2.8. Outcome measures

### 2.8.1. Primary outcome

The primary outcome was prostate cancer mortality at a median ten years after start of follow up; analysis of this outcome has been reported (Martin, 2018). **The primary outcome for the 15-year analysis is definite or probable prostate cancer mortality after a median 15 years of follow-up,** which was originally pre-specified in the secondary outcomes (see below).

Time zero for this outcome is the list date for the man's GP practice. Failure time, or censoring time, is the date on which a man dies, on which the man has left England and Wales, or the dataset census date for the current analysis (31 March 2021).

### 2.8.2. Secondary outcomes

The following were secondary outcomes included the original statistical analysis plan (Metcalfe et al, 2016); these are the pre-specified outcome measures now being addressed after a median of 15 years follow-up.

1) All-cause mortality at 10 and 15 years after start of follow up

2) Definite or probable prostate cancer mortality at 15 years

3) Disease stage and grade at diagnosis

The primary outcome for the 15-year analysis is definite or probable prostate cancer mortality at median 15 years follow-up. We will add the diagnosis of prostate cancer metastasis as a secondary outcome, although this and proceeding with (3) Disease stage and grade at diagnosis, are dependent on being able to secure good quality data from routine sources on these outcomes. If some centres are only able to provide partial data (i.e. substantially less complete than other centres) on an outcome, we will present the findings both with and without such centres included. The definition of 'partial data' will be agreed and published online in advance of outcome analyses being conducted.

CAP study estimates will be used in separate work (not covered by this plan) aimed at estimating age-specific lead time and over-diagnosis rates, and the projected lifetime effectiveness and cost-effectiveness and cost-effectiveness of alternative UK-focussed PCa screening options.

## 3. GENERAL ANALYSIS CONSIDERATIONS

### 3.1. Analysis populations

The primary analysis set is all men aged 50 to 69 years registered with a participating practice on the date when the patient list was retrieved (the "list date"). Men were excluded as described in Section 2.4.2.

### 3.2. Census and notification dates

The census date for the current analysis is 31 March 2021. All outcome events occurring up to and including the census date, and which we are notified of by the 30th September 2021, will be included in the dataset extracted and locked for the current analysis.

### 3.3. Derived variables

To allow derived variables to be validated, they will be generated as part of the analysis code, with explanatory comments.

### 3.4. Procedures for missing data

Dates missing the day will be imputed as the 15th of the month. There will be no further imputation of missing data in the primary analysis of clinical effectiveness.

### 3.5. Clustering

General practices were the unit of randomisation in this cluster randomised trial, with the randomisation stratified by clusters of neighbouring practices. Any variation between randomisation clusters and between practices in the men's outcome rates will be accommodated using randomisation cluster and practice-level random effects (i.e. a three-level model).

# 4. ASSESSMENT OF STUDY QUALITY

## 4.1. Eligibility checks

Patients already diagnosed with prostate cancer on the list date were identified through cancer registry data. Details of men were removed from the study database as soon as we were aware of their active objection to being included in the study. Details of men excluded by our consent procedure (see protocol), were not transferred from the ProtecT to CAP databases.

## 4.2. Data validation

Death due to prostate cancer is validated by an independent cause of death committee.

## 4.3. Study completion

Follow up is passive from each participant's point of view and consequently follow-up is completed for almost all men. One exception is men who emigrate: we censor follow-up for these men on the date when we become aware of them having emigrated.

## 5. ANALYSIS OF EFFECTIVENESS

### 5.1. Summary of primary and secondary outcomes

All estimates and graphical presentations will use the full data available to the end of follow-up once a median 15 years follow-up has been achieved (census date: 31 March 2021); follow-up of individual men will not be truncated at 15 years.

The cumulative incidence of prostate cancer will be presented for the two intervention groups (Appendix, **Figure 1**), for all diagnoses, for different Gleason scores / grade groups separately, and for different disease stages (Appendix, **Supplementary Figures A and B**). Stage and grade at diagnosis will be presented as frequency tables, comparing the two intervention groups (Appendix, **Table 1**).

The combined endpoint "Definite, probable, and treatment-related prostate cancer mortality" will be summarised for each intervention group at 10 and 15-year survival (estimated using the Kaplan-Meier method) with 95% confidence intervals (Appendix, **Table 2**). Cumulative incidence curves will be presented for each intervention group (Appendix, **Figure 2**). Similar statistics will be presented for all-cause mortality.

Note that we have previously presented prostate cancer diagnosis and prostate cancer mortality up until 15 years. There are additional follow-up data available to this analysis for all time-points beyond seven years post-randomisation. In addition, the data previously presented are subject to small changes due to continued updates from NHS digital, the Office for National Statistics (ONS), and Public Health England (PHE). This explanation will be included in the report of the current analysis.

### 5.2. Primary analysis

The following Poisson regression model (1) incorporates the duration of follow-up for each man i by regressing rates $\lambda_{ij}$ on covariates where j is the man's current age group.

$$\log\left(\lambda_{ij}\right) = \lambda_{0j} + y_{0r} + z_{0p} + \beta_1 x_{1i}$$
$$y_{0r} \sim N(0, \sigma_r) \qquad\qquad (1)$$
$$z_{0p} \sim N(0, \sigma_p)$$

Variation in outcome between randomisation strata r=1,…,R (neighbouring groups of GP practices) will be accommodated by standard deviation $\sigma_r$ of a level 3, zero mean, normally distributed random effect $y_{0r}$, and variation in outcome between GP practices p=1,…P will be accommodated as standard deviation $\sigma_p$ of a level 2 zero mean normally distributed random effect.

As the incidence of prostate cancer diagnosis varies greatly by age, each man's follow-up will be divided into the following current age-groups according to a lexis-diagram approach: 59 years or younger, 60-64 years, 65-69 years, 70-74 years, 75-79 years and 80 years or older. With a separate average baseline rate $\lambda_{0j}$ for each age group j, the assumption of a constant baseline rate will be reasonable for each separate age group separately.

The intervention effect will be estimated as a rate ratio $\exp(\beta_1)$, the coefficient for random allocation $x_{i1}$ with value 0 for allocation to the comparison group and value 1 for allocation to the intervention group. These estimates will be presented with the prostate cancer mortality rate for each allocated group, after median study follow up of 10 years (corresponding to the primary analysis presented in Martin et al, 2018) and 15-years (Appendix, **Table 3**).

### 5.3. Secondary analyses

The analysis in section 5.2 will be adapted to the analysis of other mortality measures.

The intervention effect on the rate of prostate cancer mortality will be estimated separately for the first ten years following the randomisation date, and for the subsequent years of follow-up. These estimates will be presented with their 95% confidence intervals, and a test of the null hypothesis that the intervention effect remains constant over the median 15 years follow-up. This is a similar approach to that taken by Schröder et al (2014) in analysing the ERSPC 13 years follow-up data, with an increase in the size of the screening effect observed from a risk ratio of 0.88 over the first 0-4 years to 0.72 during years 8-12.

Statistical methods will be employed that use random allocation as an instrumental variable, to estimate the effect of the invitation to the prostate check clinic in those who accept the invitation and attend the prostate check clinic. We will employ a generalized method of moments estimator, which takes advantage of the random allocation as a strong instrumental variable, to compare those men in the intervention group who attended the prostate check clinic, to the comparable men in the control group who would have attended the clinic if invited (Baum, 2013). Robust standard errors will be employed to accommodate any clustering of outcomes by GP practice. This analysis will employ Stata's `ivpoisson` command, with the generalized method of moments estimator, multiplicative errors, and robust standard errors to allow for clustering:

```
ivpoisson gmm pcadth (test = rand) [pw=w],
                          exp(exposure) mult vce(cluster practice_id) irr
```

Where `test` indicates those men in the intervention group who attend the clinic, and `rand` indicates the randomly allocated group. A key assumption underpinning this approach is that the subsequent rate of prostate cancer mortality is the same in the men who do not attend the clinic in the intervention group and in those men in the comparison group who would not have

11

attended the clinic if invited (Metcalfe, 2013). This instrumental variable analysis will be applied to all outcome measures in **Table 3** (see Appendix).

To assist with the interpretation of the study results, **Table 4** (see Appendix) will present prostate cancer diagnoses and prostate cancer deaths for men in the intervention group, against their findings in screening and the subsequent diagnostic pathway.

### 5.4. Pre-specified sub-group analyses

Sub-group analyses will examine whether the effect of intervention on the primary outcome varies by age group at baseline (50-54, 55-59, 60-64, 65-69+ years) and by index of multiple deprivation tertile. An interaction test p-value will be used to evaluate the evidence against the null hypothesis of equal intervention effect across sub-groups. If the association of outcome rate and age group / deprivation tertile is consistent with a linear trend, advantage will be taken of this to employ a single degree of freedom interaction test (Appendix, **Table 5**).

### 5.5. Process analysis

The analysis of age at diagnosis, stage and grade of prostate cancer will focus on men diagnosed with prostate cancer only. Mean age at diagnosis will be compared between intervention groups using ordinary linear regression. The proportions diagnosed over the 15-year average follow-up with Gleason scores of 6 or less, 7, and 8 or more (or Grade Groups 1, 2 and 3+ if the available data allow), or diagnosed with clinical stage T1/T2 disease, clinical T3, and T4/N1/M1 stage disease will each be compared between intervention groups using ordered logistic regression. Robust standard errors will be employed to allow for variation between GP practices.

### 5.6. Sensitivity analysis

Analysis of the primary outcome will be repeated in sensitivity analyses to include: (1) definite, probable, **possible** and treatment-related prostate cancer mortality; and (2) definite and treatment-related prostate cancer mortality (both estimates presented in text).

It is not anticipated that deaths due to other causes ("competing risks") will be associated with prostate cancer disease but, as deaths due to other causes will be substantial, we will present in the report text an estimate of the screening effect on the primary outcome with competing risks accommodated (Fine & Gray, 1999). We do not expect that the risk of deaths due to other causes will differ between allocated groups, but we will tabulate the data to allow this assumption to be tested (Appendix, **Supplementary Table A**).

If it is not possible for the Cause of Death Committee to consider a number of deaths (i.e. due to COVID-19 measures), the impact of this on the estimated intervention effect on the primary outcome will be assessed using our estimates of death certificate accuracy (Turner et al 2016, Gilbert et al 2016).

As described in Section 2.8.2, if some centres are only able to provide partial data for the measures dependent on routine data (i.e. substantially less complete than other centres), we will consider presenting the findings both with and without such centres included.

Should any of the management groups in the ProtecT trial be shown to be superior at 15-year median follow-up (i.e. reducing mortality), then any difference in prostate cancer or all-cause mortality between intervention and comparison groups will be less apparent than would be expected had a screening programme taken place when the optimal treatment(s) were the standard of care. In this case the beneficial effect on mortality of such an "optimal" screening programme, based on the (unbiased) treatment effect estimates from the ProtecT trial and the (unbiased) effect estimates from the CAP study will be the subject of a separate modelling study.

**REFERENCES**

Baum CF, Schaffer ME, Stillman S (2003). Instrumental variables and GMM: Estimation and testing. Stata Journal 3: 1-31.

Fine JP, Gray RJ (1999). A proportional hazards Model for the subdistribution of a competing risk. Journal of the American Statistical Association, 94:496-509

Gilbert R, Martin RM, Donovan J, et al (2016). Misclassification of outcome in case–control studies: Methods for sensitivity analysis. Statistical Methods in Medical Research 25: 2377– 93.

Martin RM, Donovan JL, Turner EL, et al (2018). Effect of a Low-Intensity PSA-based Screening Intervention on Prostate Cancer Mortality. The CAP Randomised Clinical Trial. JAMA 319:883-895.

Metcalfe C. (2013).  Can the Results of the European Randomized Study of Screening for Prostate Cancer Be Decontaminated? European Urology http://dx.doi.org/10.1016/j.eururo.2013.08.058

Metcalfe et al. (2016). CAP: Cluster randomised triAl of PSA testing for Prostate cancer Statistical Analysis Plan: version 1.5: https://research-information.bristol.ac.uk/files/84296994/20160726_CAP_analysis_plan_1_5_signed.pdf

Schröder FH, Hugosson J, Roobol MJ et al (2009). Screening and prostate cancer mortality in a randomized European study. New England Journal of Medicine 360:1320-8.

Schröder FH, Hugosson J, Roobol MJ et al (2014). Screening and prostate cancer mortality: results of the European randomised study of screening for prostate cancer (ERSPC) at 13 years of follow-up. Lancet 384:2027-35.

Turner EL, Metcalfe C, Donovan JL, et al. (2016). Contemporary accuracy of death certificates for coding prostate cancer as a cause of death: Is reliance on death certification good enough? A comparison with blinded review by an independent cause of death evaluation committee. British Journal of Cancer 115:90–4

Turner EL, Metcalfe C, Donovan JL, et al (2014). Design and preliminary recruitment results of the cluster randomised trial of PSA testing for prostate cancer (CAP). British Journal of Cancer 110:2829-2836.

Williams NJ, Hill EM, Ng SY, Martin RM, Metcalfe C, Donovan JL, Evans S, Hughes LJ, Davies CF, Hamdy FC, Neal DE, Turner EL. (2015). Standardisation of information submitted to an endpoint committee for cause of death assignment in a cancer screening trial – lessons learnt from CAP (cluster randomised trial of PSA testing for prostate cancer). BMC Medical Research Methodology 15:6.

**APPENDIX 1**

**Figure 1. Incidence of prostate cancer** Cumulative incidence of prostate cancer in the intervention (solid line) compared to control (long dash line) groups  over the 15 years median follow-up

**Figure 2a. Prostate cancer and treatment related mortality** Cumulative incidence of definite and probable prostate cancer and intervention related mortality in the intervention (solid line) compared to control (long dash line) groups

**Figure 2b All-cause mortality** Cumulative incidence of all deaths in the intervention (solid line) compared to control (long dash line) groups

**Supplementary Figure A.** Cumulative incidence of prostate cancer in the intervention (solid line) compared to control (long dash line) groups: (i) Gleason score 6 or less, (ii) Gleason score 7, (iii) Gleason score 8+

**Supplementary Figure B.** Cumulative incidence of prostate cancer in the intervention (solid line) compared to control (long dash line) groups: (i) T1/2 N0 M0 (ii) T3 N0 M0, (iii) T4 or N1 or M1

**Table 1.** Characteristics of prostate cancer cases at the time of diagnosis

| | Control group | Intervention group | Intervention group | |
| --- | --- | --- | --- | --- |
| | | | Attended prostate check clinic | Did not attend prostate check clinic |
| | | | n = | n = |
| | n = | n= | | |
| **Clinical features at diagnosis of prostate cancer: after the initial 18 months of follow-up** | | | | |
| Mean age (standard deviation) | | | | |
| **Gleason Score , n (%)*** | | | | |
| ≤6 | | | | |
| 7 | | | | |
| ≥8 | | | | |
| *Missing* | | | | |
| **Stage, n (%)*** | | | | |
| T1/T2 | | | | |
| T3 | | | | |
| T4/ M1/N1 | | | | |
| *Missing* | | | | |
| **Clinical features at diagnosis of prostate cancer: initial 18 months of follow-up** | | | | |
| Mean age (standard deviation) | | | | |
| **Gleason Score, n (%)*** | | | | |
| ≤6 | | | | |
| 7 | | | | |
| ≥8 | | | | |
| *Missing* | | | | |
| **Stage, n (%)*** | | | | |
| T1/T2 | | | | |
| T3 | | | | |
| T4/ M1/N1 | | | | |
| *Missing* | | | | |

*Column percentage of diagnosed men in the indicated group and who have data recorded for this variable.

16

**Table 2.** Prostate cancer specific survival and overall survival (Kaplan-Meier estimates) at 10 years and 15 years post-randomisation by random allocation and intention-to-screen estimate of the difference between groups

| | Intervention group | | Control group | | |
| --- | --- | --- | --- | --- | --- |
| | Deaths | Probability of survival (95% CI) | Deaths | Probability of survival (95% CI) | Survival difference (95% CI) |
| **Definite or probable prostate cancer death or IRD** | | | | | |
| 15-year survival | | | | | |
| 10-year survival | | | | | |
| **All-cause mortality** | | | | | |
| 15-year survival | | | | | |
| 10-year survival | | | | | |

CI denotes confidence interval; IRD = intervention related death

**Table 3.** Prostate cancer specific mortality and all-cause mortality by random allocation: intention-to-screen estimate and instrumental variable estimate of the effect of screening in men allocated to and attending the prostate check clinic

| | Intervention group | | Control group | | | | Effect of screening amongst those attending clinic (N=xxx,xxx) | |
|---|---|---|---|---|---|---|---|---|
| | Deaths | Deaths per 1000 person years (95% CI) | Deaths | Deaths per 1000 person years (95% CI) | Rate ratio (95% CI) | p-value[1] | Rate ratio (95% CI) | p-value |
| **Definite or probable prostate cancer death or IRD** | | | | | | | | |
| At 15 years median follow-up | | | | | | | | |
| At 10 years median follow-up[2] | | | | | | | | |
| First ten years of each man's follow-up | | | | | | | | |
| Subsequent follow-up | | | | | | | | |
| **All-cause mortality** | | | | | | | | |
| At 15 years median follow-up | | | | | | | | |
| At 10 years median follow-up[2] | | | | | | | | |

CI denotes confidence interval; IRD = intervention related death

1. Likelihood ratio test of the null hypothesis "no difference in prostate cancer mortality between the groups", adjusted for current age

2. Subject to small changes compared to previously published estimates due to corrections received from NHS digital, the Office for National Statistics, and Public Health England

18

**Table 4.** Clinical outcomes in the CAP intervention group over 15 years median follow-up by diagnostic pathway findings

| | Total N | Prostate cancer diagnosis | Prostate cancer death |
|---|---|---|---|
| PSA test non-attenders | | | |
| **PSA test attenders** | | | |
| No valid test | | | |
| No result | | | |
| PSA<3ng/ml (screen negative) | | | |
| PSA 20ng/ml+ | | | |
| **PSA 3+ but <20ng/ml** | | | |
| **(eligible for a biopsy)** | | | |
| No biopsy | | | |
| **Biopsy** | | | |
| Negative biopsy result | | | |
| **Positive biopsy result** | | | |

**Table 5.** Planned sub-group analyses of prostate cancer specific mortality[1] over median 15 years follow-up

| | Intervention group | | Control group | | | |
|---|---|---|---|---|---|---|
| | Deaths | Deaths per 1000 person years (95% CI) | Deaths | Deaths per 1000 person years (95% CI) | Rate Ratio (95% CI) | p-value[2] |
| **Age at baseline** | | | | | | |
| 50-54 | | | | | | |
| 55-59 | | | | | | |
| 60-64 | | | | | | |
| 65-69+ | | | | | | |
| **Index of multiple deprivation (England)** | | | | | | |
| Tertile 1 | | | | | | |
| Tertile 2 | | | | | | |
| Tertile 3 | | | | | | |
| **Index of multiple deprivation (Wales)** | | | | | | |
| Tertile 1 | | | | | | |
| Tertile 2 | | | | | | |
| Tertile 3 | | | | | | |

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

2. Likelihood ratio interaction test of the null hypothesis of no difference in the comparison across the different subgroups

**Supplementary Table A.** Underlying causes of death (as recorded on the death certificate) in intervention versus control groups at 15-year median follow-up (not including prostate cancer deaths).

| Cause of death | Intervention n (%) | Control n (%) |
|---|---|---|
| Any (not including prostate cancer deaths) | | |
| Other cancers | | |
| Ischaemic heart disease | | |
| Stroke | | |
| Other circulatory disease | | |
| Respiratory disease | | |
| Digestive disease | | |
| Infectious disease | | |
| Blood, immune, endocrine | | |
| Nervous system disease | | |
| Accident | | |
| Other | | |