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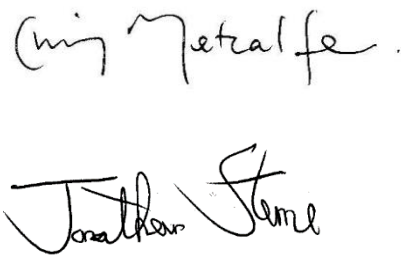
Bristol Randomised Trials Collaboration (BRTC)

CAP: Cluster randomised trial of PSA testing for prostate cancer

Statistical Analysis Plan

Version 1.5 (26th July 2016)

The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents			
Name	**Role**	**Signature**	**Date**
Chris Metcalfe & Jonathan Sterne	Author		19/08/2016
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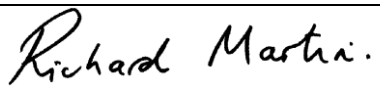
Richard Martin	Chief Investigator		31/08/2016

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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)
ProtecT	PROstate TEsting for Cancer and Treatment
PSA	Prostate Specific Antigen
TNM	Tumour, Nodes, Metastases
UK	United Kingdom

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 main results from **the CAP study (Cluster randomised trial of testing for prostate cancer).**

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 (version 7, 29 May 2012) 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.

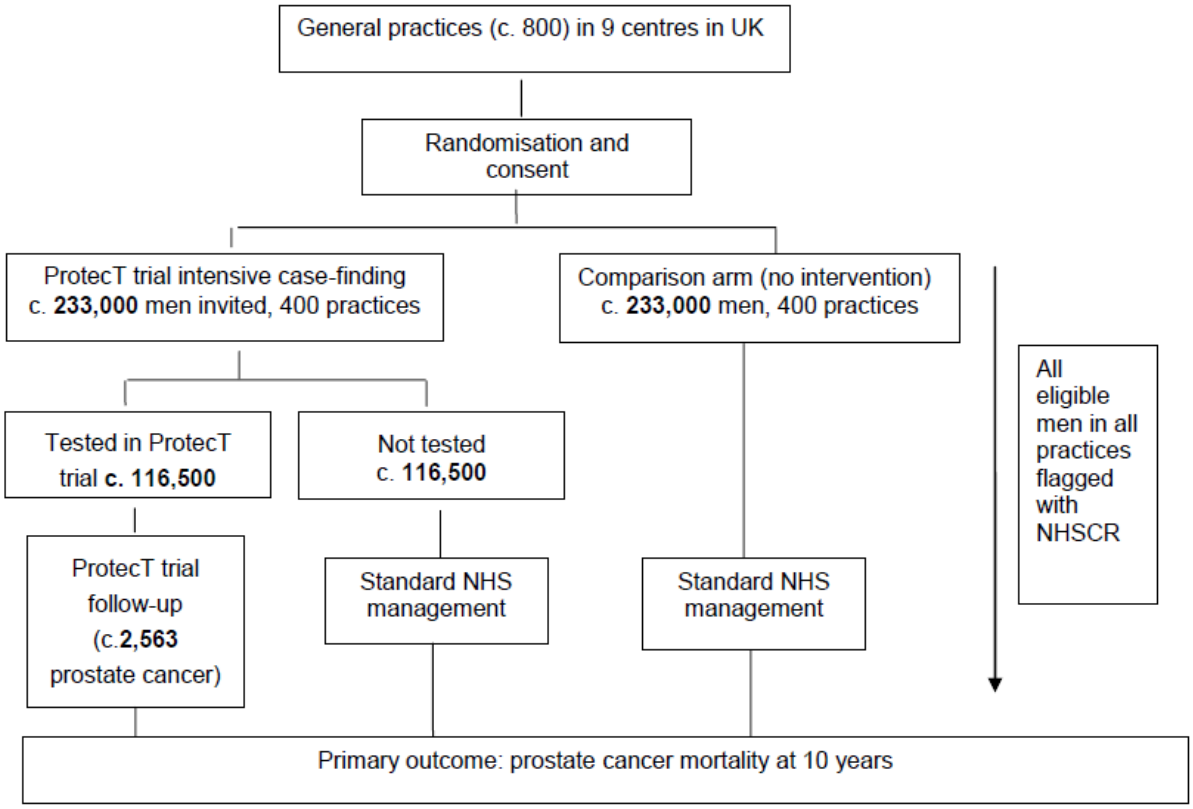
2.1. Trial aims and objectives

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 screen 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.

2.2. Trial design and configuration



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 are eligible to participate, and are 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 is an 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 are invited to undergo a diagnostic biopsy. Those men found to have clinically localised prostate cancer are invited to have their treatment randomised in the ProtecT trial of surgery, radiotherapy, and conservative management.

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

2.6. Randomisation procedures

The CaP study is cluster randomised. At each study centre, neighbouring groups of eight to twelve GP practices are block-randomised in a 1:1 ratio to PSA testing as part of the ProtecT study, or to NHS usual care in the comparison arm. When the group includes an odd number of practices, the greater number are allocated to the intervention arm. This randomisation is done by an independent statistician (S Brookes) with no other involvement with the study. The randomisation precedes approaches to the GP practices; practices are invited to participate in the arm of the study they are allocated to.

Allocation is based on random numbers generated using the contemporary version of Stata statistical software (College Station, TX, USA).

2.8. Blinding

Members of the cause of death committee see patient vignettes, prepared to obscure the study arm the patient is in. Hence decisions about the cause of death are made blind to study arm.

2.9. Trial committees

The CaP study has a Data Monitoring Committee (DMC), chairperson Professor Lars Holmberg, which meets annually. The chairperson for the CaP study Cause of Death Committee is Professor Peter Albertsen.

2.10. Outcome measures

2.10.1. Primary outcome

The primary outcome is prostate cancer mortality at a median ten years after start of follow up.

This includes those deaths judged as definitely or probably due to prostate cancer by the cause of death committee. Deaths due to the treatment of prostate cancer are included, again as judged by the cause of death committee. “Ten years” is the point in time when the median follow-up period for men in the study is ten years, which is anticipated to be the end of March 2016. Allowing a four month period for information on outcome events to reach us from the UK National Statistics Office, we propose to include all primary outcome events which have occurred on or before the 31st March 2016, and which we have received notification of by the 31st July 2016. Only outcome events for which we receive notification from the UK National Statistics Office will be included in the main analyses.

2.10.2. Secondary outcomes

1) All-cause mortality at 5,10 and 15 years after start of follow up
2) Definite or probable prostate cancer mortality at 5 and 15 years
3) Disease stage and grade at diagnosis
4) Cost-effectiveness
5) Health related Quality of Life

Health related Quality of Life has been examined in separate sub-studies, and will not be considered further in this analysis plan. Similarly, cost-effectiveness will be the subject of a separate plan.

2.11. Interim analysis

Interim analyses by trial arm will be conducted when requested by the DMC. These are prepared by the study DMC statistician (C Metcalfe) and shared only with the DMC in the first instance. There are no pre-defined formal stopping rules.

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 is retrieved (the "list date"). Men are excluded as described in Section 2.4.2.

3.2. Derived variables

The primary outcome measure is a binary variable, distinguishing those individuals who definitely or probably died of prostate cancer, or treatment for prostate cancer. Time zero 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 the country, or the dataset closure date.

3.3. 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.

3.4. Study centre effects

The primary analysis is adjusted for randomisation cluster. This accommodates any between-centre differences in the outcome rate. ~~In addition, differences in the intervention effect by study centre are examined as one of the pre-specified subgroup analyses (section 6.5 below).~~

3.5. Competing risks

As age is the only strong risk factor that prostate cancer mortality has in common with other causes of death, distortion of our results due to "competing risks" is unlikely.

3.6. Clustering

General practices are the unit of randomisation in this cluster randomised trial. Any variation between practices in the men's outcome rates will be accommodated by separating that variation from that between individual men, using practice-level random effects.

4. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

4.1. Disposition

The recruitment of GP practices, and the flow of patients through the trial, will be summarised in a CONSORT diagram for cluster randomised trials (Campbell, 2004) that includes eligibility, reasons for exclusion, numbers randomised to the two intervention groups, losses to follow up and the numbers analysed.

4.2. Baseline characteristics

The following comparisons are made between intervention and comparison arm practices, using data from routine primary care statistics:

- Practice list size
- IMD score (separately for England and Wales, lower level super output area)
- Urban location
- Prevalence of all cancer
- Prevalence of diabetes
- Prevalence of obesity
- Prevalence of CHD

Age on list date is the only baseline variable available for individual men. This is compared between the two arms of the study using a random effects model.

5. ASSESSMENT OF STUDY QUALITY

5.1. Eligibility checks

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

5.2. Data validation

The primary outcome measure is validated by an independent cause of death committee.

5.3. 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.

5.4. Compliance

Data are being collected on those intervention arm men who undergo a PSA test as part of the study.

5.5. Protocol deviations

GP practices which do not agree to participate, having been randomised, are excluded from the study and analysis.

In an effort to identify comparison arm practices who increase their PSA testing once recruited to the study, we will look at when prostate cancer diagnoses occur for each practice. A peak in diagnoses in the period after a comparison arm practice joins the study may indicate that practice has been prompted to increase the use of PSA testing.

6. ANALYSIS OF EFFECTIVENESS

6.1. Men who move GP practice

Patients are analysed according to the allocation of their GP practice. Duplicate records of men who have moved practices are removed; if the man moves between arms of the study, the record at the ProtecT practice is retained, otherwise the record collected at the earlier date is retained. The number of duplicates and the action taken is recorded.

6.2. Summary of primary and secondary outcomes

The combined endpoint "Definite, probable, and treatment-related prostate cancer mortality" will be summarised for each study arm as 5 and 10-year survival (estimated using the Kaplan-Meier method) with 95% confidence intervals. Nelson-Aalen cumulative hazard curves will be plotted in order to provide a graphical check of the proportional hazards assumption. If there is evidence of a difference between study arms, the number needed to invite (NNI; study question & policy context) in order to prevent one prostate cancer death will be calculated as one divided by the absolute difference in prostate cancer deaths between the randomised intervention and comparison groups. Following the ERSPC's lead we will also present the number needed to detect (NND; with the assumption that these men are then treated), calculated as the NNI multiplied by the excess incidence of prostate cancer in the intervention group (Schroder 2009, 2014). In addition we will calculate the number needed to attend (NNA, corresponding to number needed to screen) calculated as one divided by the absolute difference in prostate cancer deaths between those men allocated to an invitation to a prostate check clinic and who attended, and those men in the comparison arm who would have attended had they been invited (this latter value will be estimated using the CACE approach described in section 6.4; Dunn, 2002). The NNI, NNA and NND will be presented in the text of the main results paper.

Similar statistics will be presented for ~~prostate cancer mortality at other pre-specified time points, and for~~ all-cause mortality.

Stage and grade at diagnosis will be presented as frequency tables, comparing the two arms of the study.

6.3. Primary analysis

The null hypothesis for the primary analysis is "no difference in definite, probable and treatment related prostate cancer mortality between men at GP practices inviting 50 to 69 year olds to a undergo a single PSA test, and men at GP practices following current NHS guidance". The following Poisson regression model (1) incorporates the duration of follow-up for each man i by regressing rates λ_{ij} on covariates where j is the man's current age group.

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

Variation in outcome between randomisation strata r=1,…,R (neighbouring groups of GP practices) will be accommodated by standard deviation σ_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 σ_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. We will combine the 75-79 and 80+ age groups if there are too few events to permit separate analysis for the 80+ group. With a separate average baseline rate λ_{0j} for each age group j, the assumption of a constant baseline rate will be reasonable for each separate age group separately.

The treatment 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.

Our initial intention to further divide each man's follow-up by current calendar period proved problematic for estimation in interim analyses for the DMC and so was abandoned.

It is not anticipated that deaths due to other causes ("competing risks") will be associated with prostate cancer disease, nor will the risk of their recurrence differ between intervention arms. Hence no special measures will be taken to account for competing risks.

6.4. Secondary analyses

The analysis in section 6.3 will be adapted to the analysis of other mortality measures.

Analysis of the primary outcome will be repeated including (1) definite, probable, **possible** and treatment-related prostate cancer mortality and (2) definite and treatment-related prostate cancer mortality.

As has been done for the ERSPC study (Schroder 2009; Bokhurst 2013) 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. In contrast to the ERSPC study, we will not attempt to control for contamination, due to the very strong assumptions required for this analysis (Metcalfe, 2013). Moreover we will not have data to indicate which men in the control arm have been screened for prostate cancer.

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 arm who attend the prostate check clinic, to the comparable men in the control arm who would attend 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 arm. 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 arm and in those men in the comparison arm who would not have attended the clinic if invited (Metcalfe, 2013).

The instrumental variable analyses described above will be done for all outcome measures in Table 2.

6.5. Pre-specified sub-group analyses

Sub-group analyses will examine whether the intervention effect varies by age group at baseline (50-54, 55-59, 60-64, 65-69+ years), and by the index of multiple deprivation for a man's area of residence (subgroups defined as tertiles for the cohort as a whole, but with Wales and England calculated separately)~~study centre~~. 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 is consistent with a linear trend, advantage will be taken of this to employ a single degree of freedom interaction test.

6.6. 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 study arms using ordinary linear regression. The proportions diagnosed over the ten-year average follow-up with Gleason scores of 6 or less, 7, and 8 or more, or diagnosed with clinical stage T1/T2 disease, clinical T3, and T4/N1/M1 stage disease ~~grades 3+3, 3+4, 4+3, 4+4, 4+5, 5+4 and 5+5 is~~ will each be compared between study arms using ordered logistic regression. ~~This approach is adapted to an analysis of disease stage, based on the TNM system. For this latter analysis the~~

~~patient is classified to the most advanced disease stage applicable from T1, T2, T3, T4, N1, M1.~~ Robust standard errors will be employed to allow for variation between GP practices.

6.7. Sensitivity analysis

If imbalances between the participating practices allocated to each study arm are apparent, then prior to the primary analysis, the study PIs will list these characteristics, which will be added as further covariates in the regression model. Such analysis will be reported as a sensitivity analysis: the primary analysis will remain unchanged.

Should any of the treatment arms in the ProtecT trial be shown to be superior (i.e. to lead to reduced mortality), then any difference in prostate cancer or all-cause mortality between intervention and comparison practices will be lower than would be expected if a screening programme had taken place when the optimal treatment(s) were the standard of care. In this case we will estimate 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) overall effect estimates from the CAP study.

We will repeat the comparison of Gleason score at diagnosis of prostate cancer between the intervention and comparison groups, with the Gleason score reduced to a binary distinction between scores of 7 and below versus 8 and above. There is some evidence that whilst UK histopathologists have remained consistent in their use of the 7/8 distinction over the study period, they may have increased their use of a score of 7 rather than 6 during that time (Oxley 2015).

We will re-estimate the risk ratios estimated using the instrumental variable approach described in Section 6.4 above under an alternative definition of the instrumented variable: attended the PCC clinic, had blood taken for a PSA test, and received a result which could be acted upon.

We will recalculate the incidence of prostate cancer in the intervention arm, including those diagnoses we became aware of due to ProtecT diagnostic procedures, but of which we were not notified by the UK National Office of Statistics.

~~As has been done for the ERSPC study (Schroder 2009; Bokhurst 2013) statistical methods are employed that use random allocation as an instrumental variable, to estimate the effect of testing in those who do undergo PSA testing (Palmer, 2011). This estimate can be used to predict the overall effect of a screening programme under different assumptions about PSA uptake. In contrast to the ERSPC study, we do not attempt to control for contamination, due to the very strong assumptions required for this analysis (Metcalfe, 2013).~~

6.8. Scotland

We are applying for anonymised data on men in intervention (ProtecT) and control practices in Scotland. These data will be for men fitting our eligibility criteria, and will include outcome data for a ten-year period. The key difference between these Scottish data and the data we are collecting for the CAP study in England and Wales is that it will not be possible to validate the cause of death for Scottish men; we will need to rely on the death certificates. Consequently, for the primary CAP analysis, we will analyse and present the data for Scottish men separately, but using the same statistical approach as described in the statistical analysis plan. If a case can be made for the Scottish data being of acceptable quality, then it will be included in a possible future meta-analysis of data from the CAP and the ERSPC.

7. CHANGES SINCE VERSION 1.4

Substantive changes since the previous version have been highlighted in green. In summary these are:

- On the advice of the Trial Steering Committee (January 2016, see Appendix 2), we will present the number needed to invite, the number needed to attend, and the number needed to detect as described in Section 6.2.
- We previously planned to present an estimate of the effect of screening in those who attend the prostate check clinic in a sensitivity analysis. On the advice of the Trial Steering Committee (January

2016), we will now present such estimates for all the outcomes in Table 2 as secondary analyses. Consequently we have pre-specified these analyses in more detail in Section 6.4. Furthermore, we are now specific that the aim of these analyses is to estimate the effect of the intervention, an invitation to a prostate check clinic, in those men who attend the clinic. These estimates will be calculated using an instrumental variable approach, to avoid the known biases of the per protocol approach.

- We now plan a sub-group analysis by area index of multiple deprivation, rather than by study centre, as described in Section 6.5.
- We now make it clear that we are also interested in comparing age at prostate cancer diagnosis between the two study arms, as described in Section 6.6. We have added a sensitivity analysis looking at the proportion of men diagnosed with Gleason score of 8, compared between the intervention and comparison groups, to avoid confounding by "Gleason drift".
- Outlines of the Figures and Tables to be included in the primary results paper are given in the Appendix.

In addition there have been minor amendments to grammar.

REFERENCES

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

Bokhorst LP, Bangma CH, van Leenders GJ, et al. (2013). PSA-based prostate cancer screening: reduction of prostate cancer mortality after correction for nonattendance and contamination in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). European Urology http://dx.doi.org/10.1016/j.eururo.2013.08.005

Campbell MK, Elbourne DR, Altman DG. (2004). CONSORT statement: extension to cluster randomised trials. BMJ 328: 702-8.

Dunn G. (2002). Estimating the causal effects of treatment. Epidemiologia e Psichiatria Sociale 11:206-215.

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

Oxley J, Simpkin A, Goepel J, et al. (2015). Gleason drift in the NIHR ProtecT study. Histopathology 66:438-46.

~~Palmer TM, Sterne JAC, Harbord RM, et al. (2011). Instrumental variable estimation of causal risk ratios and causal odds ratios in Mendelian randomization analyses. American Journal of Epidemiology 173:1392-1403.~~

Schroder 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.

Schroder 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

APPENDIX 1

Figure 1. CONSORT diagram for recruitment into the Cluster Randomised Trial of Testing for Prostate Cancer (CAP), England and Wales.

Figure 2a. Incidence of prostate cancer Cumulative incidence of prostate cancer in the intervention (solid line) compared to control (long dash line) groups

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

Figure 2d Secondary analysis Cumulative incidence of definite, probable and possible prostate cancer and intervention related mortality in the intervention (solid line) compared to control (long dash line) groups

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

			Intervention arm	
	Control arm	Intervention arm	Attended prostate check clinic	Did not attend prostate check clinic
	n =	n=	n =	n =
Mean age at diagnosis (standard deviation)				
Grade at diagnosis (%)*				
≤6				
7				
≥8				
Missing				
Stage at diagnosis (%)*				
T1/T2 (stage I/stage II)				
T3 (stage III)				
T4/ M1/N1 (stage IV)				
Missing				

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

Table 2. 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 arm		Control arm					Effect of screening amongst those attending clinic (N=xxx,xxx)	
	Deaths	Rate per 1000 person year (95% CI)	Deaths	Rate per 1000 person year (95% CI)	Rate Difference (95% CI)	Rate ratio (95% CI)	p-value[1]	Rate ratio (95% CI)	p-value
Primary Outcome									
Definite or probable prostate cancer death or IRD									
Secondary Outcomes									
All-cause mortality									
Definite or probable or possible prostate cancer death or IRD									
Definite prostate cancer death or IRD									

CI denotes confidence interval; IRD = intervention related death

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

Table 3. Planned sub group analyses of prostate cancer specific mortality[1]

	Intervention arm		Control arm				
	Deaths	Rate per 1000 person year (95% CI)	Deaths	Rate per 1000 person year (95% CI)	Rate difference (95% CI)	Rate Ratio (95% CI)	p-value[1]
Age at baseline							
50-54							
55-59							
60-64							
65-69+							
IMD area deprivation England							
Tertile 1							
Tertile 2							
Tertile 3							
IMD area 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 MATERIAL

Supplementary Table S1. Individual and practice level characteristics at baseline

	Intervention arm	Control arm
Individual Characteristics	n= xxx,xxx men	n= xxx,xxx men
Mean age (s.d.)		
Mean IMD score England (s.d.)		
Mean IMD score Wales (s.d.)		
Urban/rural (%)**		
Practice Characteristics	n= xxx practices	n= xxx practices
Mean practice list size (s.d.)		
Number of urban practices (%)		
Number of single versus multiple partner GP practices (%)***		
Number of teaching practices (%)***		
Mean QOF score (s.d.)***		
Mean IMD score in England (s.d.)		
Mean IMD score in Wales (s.d.)		
Mean prevalence from QOF		
All cancers (s.e)		
Diabetes (s.e)		
Obesity (s.e)		
Coronary heart disease (s.e)		

s.d. = standard deviation; s.e. = standard error; *if we can obtain reliable data from HSCIC, not currently in request for whole cohort; **if we obtain reliable data from the HSCIC, ***if we obtain reliable data from QOF

APPENDIX 2

Signed extract from the Trial Steering Committee

15th MEETING OF THE PROTECT AND CAP STUDIES TRIAL STEERING COMMITTEE

London, 27th - 28th January 2016

Extract of the minutes relating to the CAP statistical analysis plan.

On day one of the meeting, there was the first presentation of the unblinded ProtecT treatment trial results. On day two, discussion focussed on the CAP trial (blinded), with particular attention to issues of contamination.

The TSC considered data on the estimated rate of PSA testing in the intervention arm (40% at the start of the median 10 year follow-up) vs the 10 year cumulative testing rate in the comparison arm (20% of the median 10 years follow-up). Based on these data, the TSC advised that the points below should be considered before unblinding of the CAP trial data for analyses.

1. We suggest that both efficacy and effectiveness should be presented in the 10 year outcomes' paper, with number need to screen (NNS) (public health context) and number needed to invite (NNI) (study question) included.

2. The TSC, therefore, recommends that the 10 year outcomes' paper should retain the ITT analysis as giving the primary estimate of the effectiveness of inviting men to undergo a PSA test, but also feature an analysis that estimates the effect of testing in those screened. This latter estimate will employ methods that use the random allocation to control bias (i.e. an instrumental variables, IV, analysis). Such an analysis is recorded as a `sensitivity' analysis in the current statistical analysis plan, but will now be given greater prominence and more detail of the methods pre-specified in a revised statistical analysis plan.

As Chair of the TSC, I confirm that these notes are a true record of issues raised at the meeting

Signed Professor Baum: .....

Date: 21/06/2016