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Bristol Randomised Trials Collaboration (BRTC)

CAP: Cluster randomised trial of testing for prostate cancer

Statistical Analysis Plan

Version 1.3 (16th December 2013)

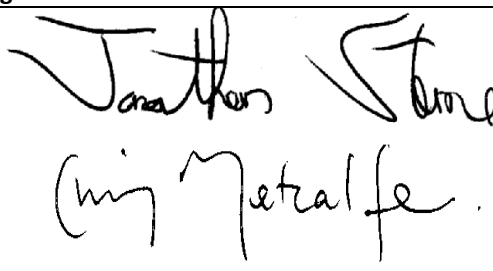

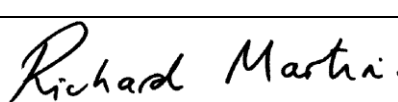
The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents			
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Abbreviations

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 analysis proposed 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 actual 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 (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

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.

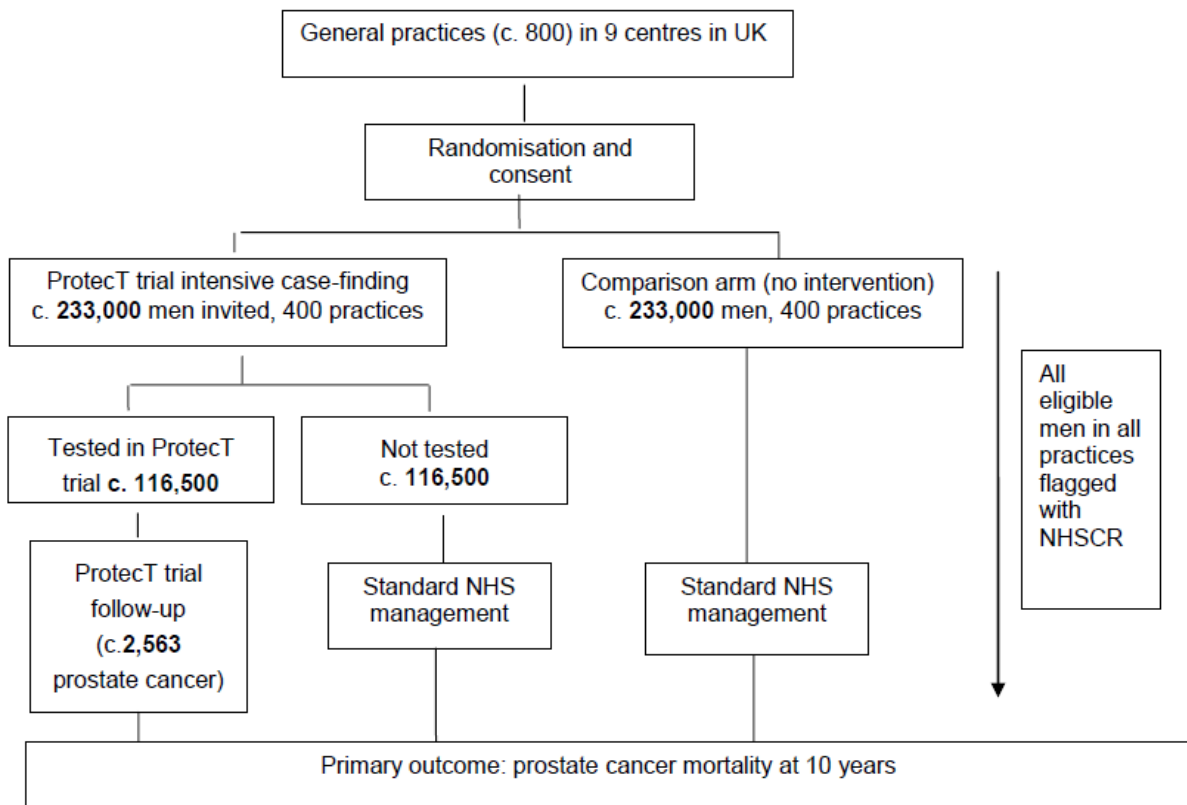
2.1. Trial aims and objectives

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. 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 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 **is** 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 CaP study Cause of Death Committee, chairperson Professor Peter Albertsen.

2.10. Outcome measures

2.10.1. Primary outcome

Prostate cancer mortality at ten years.

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; this occurs in 2016.

2.10.2. Secondary outcomes

- 1) All-cause mortality at 5,10 and 15 years
- 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 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.

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 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 resulting 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 a single point in time, which is the earliest point at which this data is reliably available 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 our 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 are censoring follow-up for these men 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. Mis-randomised patients

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

Definite, probable, and treatment-related prostate cancer mortality are summarised for each study arm as Nelson-Aalen cumulative hazard curves, and as 10-year survival (estimated using the Kaplan-Meier method) with 95% confidence intervals.

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

Stage and grade at diagnosis are 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 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.

$$\begin{aligned}\log(\lambda_{ij}) &= \lambda_{0j} + y_{0r} + z_{0p} + \beta_1 x_{i1} \\ y_{0r} &\sim N(0, \sigma_r) \\ z_{0p} &\sim N(0, \sigma_p)\end{aligned}\tag{1}$$

Variation in outcome between randomisation strata $r=1,\dots,R$ (neighbouring groups of GP practices) is 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 $p=1,\dots,P$ is 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 is 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 years or older. With a separate average baseline rate λ_{0j} for each age group j , the assumption of a constant baseline rate applies to each group separately and is consequently much more reasonable.

The treatment effect is 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 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 are taken to accommodate bias due to competing risks.

6.4. Secondary analyses

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

Analysis of the primary outcome is repeated including definite, probable, **possible** and treatment-related prostate cancer mortality. Similarly, just including definite and treatment-related prostate cancer mortality.

6.5. Pre-specified sub-group analyses

Sub-group analyses examine whether the intervention effect varies by age group (50-54, 55-59, 60-64, 65-69+ years) at baseline, and by study centre. The evidence against the null hypothesis of equal intervention effect across sub-groups is calculated as an interaction test p-value. 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, so maximising statistical power.

6.6. Process analysis

Stage and grade: This analysis focuses on men diagnosed with prostate cancer only. The proportions diagnosed over the ten-year average follow-up with Gleason grades 3+3, 3+4, 4+3, 4+4, 4+5, 5+4 and 5+5 is compared between study arms using ordered logistic regression. Robust standard errors are employed to allow for clustering. 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.

6.7. Sensitivity analysis

If imbalances are apparent between the participating practices allocated to each study arm, then prior to the primary analysis, the study PIs shall list these characteristics for adding as further covariates in the regression model.

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 shall 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.

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 (Metcalf, 2013).

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