This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

CAP study

Comparison Arm for ProtecT

Protocol v3

September 2005

Principal Investigators:

JL Donovan[1]

RM Martin[1]

FC Hamdy[2]

DE Neal[3]

Trial Co-ordinators:

SM Noble[1]

CR Metcalfe[1]

[1]Department of Social Medicine, University of Bristol, Bristol BS8 2PR
[2]University of Sheffield, Royal Hallamshire Hospital, Sheffield S10 2JF
[3]Oncology Centre, Addenbrooke's Hospital, Cambridge, CB2 2QQ

Study Coordinator and Health Economics Lead

Dr Sian Noble, Dept of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road Bristol BS8 2PR Tel: 0117 9287344, Fax: 0117 9287292, email: s.m.noble@bristol.ac.uk

Deputy Study Coordinator

Dr Chris Metcalfe, Dept of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road Bristol BS8 2PR Tel: 0117 9287326, Fax: 0117 9287325, email: Chris.Metcalfe@bristol.ac.uk

Principal Statistician

Dr Jonathan Sterne, Dept of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road Bristol BS8 2PR Tel: 0117 9287396 email: jonathan.sterne@bristol.ac.uk

Primary Care Recruitment

Dr Kerry Avery, Dept of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road Bristol BS8 2PR Tel: 0117 9287233 email: kerry.avery@bristol.ac.uk

Contents

Figures

Abbreviations

CC = Clinical Centre
SMed = Dept of Social Medicine, Bristol
SOP = Standard Operating Procedure

1. Introduction

1.1 Background to study

Few international issues in health care are as controversial as prostate cancer screening. Prostate cancer has a major impact on public health in the UK. There were over 8,500 deaths from prostate cancer in England and Wales in 1998,[1] making it the second leading cause of cancer mortality in men. The aetiology of prostate cancer remains unclear and opportunities for primary prevention are limited. Developments in diagnostic tests for prostate cancer, in particular the introduction of PSA testing, have led to increased interest in the possibility of secondary prevention through population screening. Screening to identify prostate cancer while it is localised to the gland has provoked much public and scientific attention and there is intense debate about its role in improving men's health. Current UK health policy does not advocate population screening, but the policy remains under active review by the National Screening Committee. Major concerns remain about the lack of evidence about the effectiveness of treatments (the rationale for the ProtecT treatment trial) and the potential for diagnosis and over-treatment of tumours that might never become clinically significant.
Recent publications have further fuelled the debate about population screening. The Scandinavian treatment trial showed a 50% reduction in prostate cancer mortality following radical prostatectomy compared with watchful waiting for 'early prostate cancer', but there was no significant difference in all-cause mortality,[2] and fewer than 5% presented following screening with the PSA test, thus limiting its relevance to screen-detected men.[2] An observational study of two fixed cohorts in the US showed significant increases in diagnosis and treatment of prostate cancer in intensively screened Seattle compared with non-screened Connecticut, but there was no difference in prostate cancer mortality over 11 years of follow-up.[3] While prostate cancer is clearly a serious public health problem, debate about screening is conducted in the absence of high quality evidence about its potential impact, as detailed in a recent review.[4]

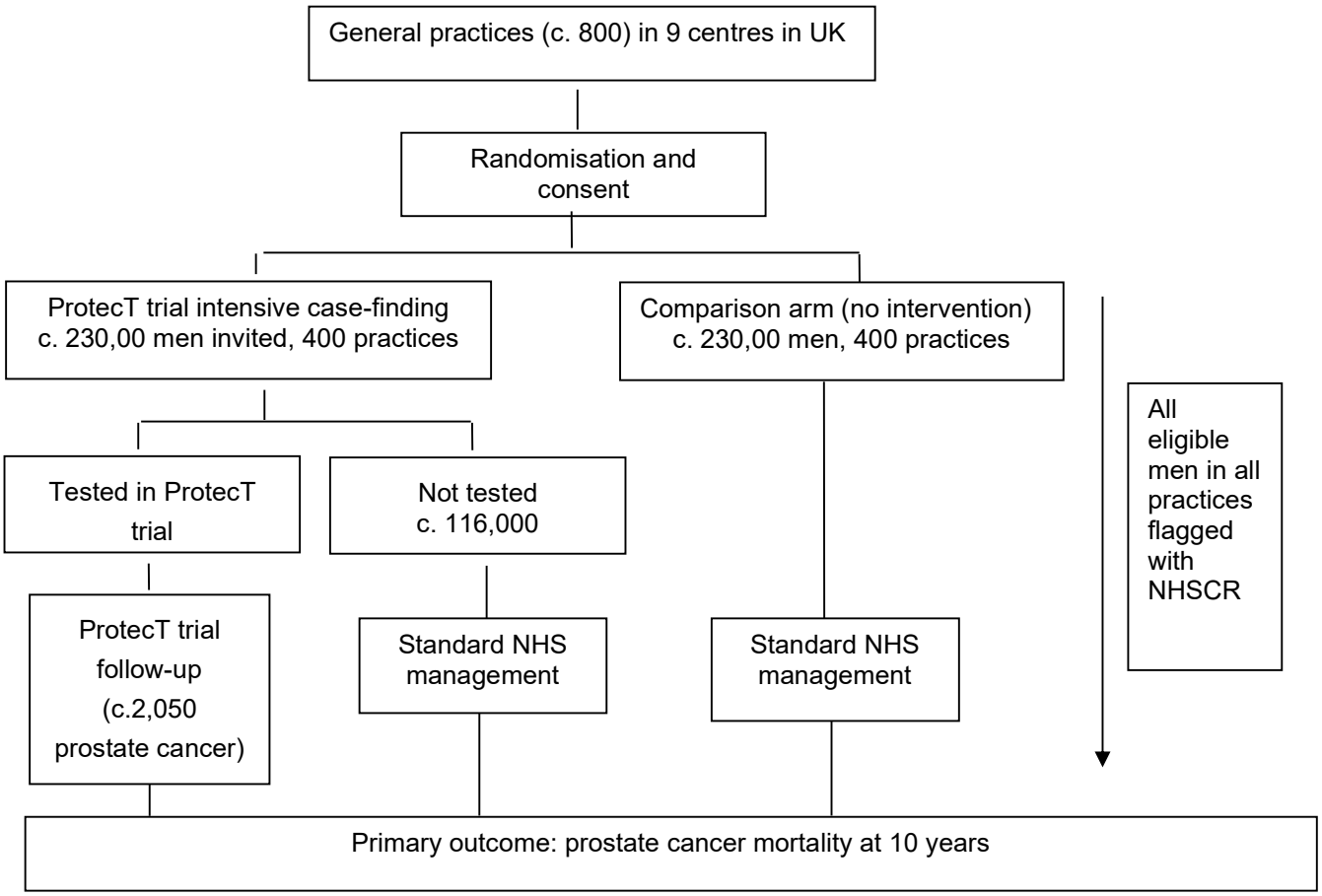
1.2 The needs for a trial now

In the UK the introduction of routine prostate cancer screening is being delayed until adequate evidence becomes available to inform policy. Trials of population screening are currently underway Europe (European Randomised Screening trial for Prostate Cancer, ERSPC[5]) and US (Prostate, Lung, Colorectal and Ovary trial, PLCO[6]). They will report combined findings around 2008.[7] The controversy over breast cancer screening demonstrates the overwhelming need for the conduct of high quality, randomised studies - some 14 years after the first trials were reported, questions over the methodological quality and size of the trials of breast cancer screening mean that arguments over its costs and benefits continue,[8] with different countries reaching different conclusions over whether such programmes are justified. The complexity of the issues involved in prostate cancer screening make it timely to extend ProtecT to allow the assessment of the potential impact of population screening for prostate cancer in the UK. The differences in aspects of design between the ProtecT extension and the ERSPC and PLCO studies in terms of the methods of recruitment, screening tests and treatments offered (see Table 1) will allow wider exploration of the issues and also provide opportunities to both pool and compare findings. The design of the ProtecT extension will lead to lower levels of contamination and more precise estimates of screening effectiveness. Further, where controversy is as great as it is in relation to prostate cancer screening, and the potential investment so large, there are considerable strategic advantages in conducting this UK trial. It will add to international understanding of the cost-effectiveness of the secondary prevention of prostate cancer, but, more parochially, assist with policy development in the UK.

Table 1 Major design aspects of the two ongoing screening trials[7] and CAP

	ERSPC	PLCO	CAP
Age range	55-69 years (core group) Some 50-54, 70-74 years	55-74 years	50-69 years
Design	Individual randomisation	Individual randomisation	Cluster randomisation
Participants	Most randomly selected from population registries. Some volunteers	Volunteers	All individuals from randomly selected general practices
PSA threshold	3.0ng/ml or 4.0ng/ml (varies by centre)	4.0ng/ml	3.0ng/ml
Screening interval	4-yearly (some 1, 2 years)	1 year	Single screen
Percent PSA raised	7-15% (varies by centre)	16%	11%
Cancers detected per 1,000 screened	11-42 (varies by centre)	Not available	12
Treatment regimen in screened group	Variable usual care (radical advised)	Variable usual care (radical advised)	Randomised (surgery, radiotherapy, active monitoring)

2. Trial design (Figure 1)



3. Aims

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.

4. Objectives

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.

5. Study design

This cluster-randomised trial consists of two arms:

a) The intervention arm - The NHS HTA funded ProtecT treatment trial. This investigates the effectiveness and cost-effectiveness of radical surgery, radical radiotherapy and active monitoring for clinically localised prostate cancer. 120,000 men aged 50-69 years in approximately 400 GP surgeries in nine UK centres (Sheffield, Newcastle, Bristol, Birmingham, Cardiff, Edinburgh, Leeds, Cambridge and Leicester) are being invited to be tested between 2001 and 2006 for the presence of prostate cancer in a process of case-finding that is almost identical to population screening.

b) The comparison arm, in which a comparable population of men in approximately 400 GP surgeries in the same UK Centres are not subject to intensive case-finding for prostate cancer.

The CAP cluster randomised control trial consists of two major components:

1) The identification and flagging with the NHS Central Register (NHSCR) and local cancer registries of i) men taking part in the ProtecT trial ii) men in the intervention arm who neither opted out nor took part in the ProtecT trial, iii) all men in the comparison arm.
2) The review of hospital case notes for men identified as having a probable or possible prostate cancer-related event.

6. Ethical aspects

6.1 Ethics

The study will be conducted according to the Declaration of Helsinki 1964, as revised in Tokyo 1975, in Venice 1983 and by the 41st World Medical Assembly, Hong Kong, September 1989.

6.2 Ethics Committee Approval

Approval has been given by Trent MREC for flagging on 12th February 2004. This approval is given under section C of the DoH 'No local researcher' guidelines. LREC approval is therefore not needed.

The Patient Information Advisory Group (PIAG) granted the study exemption from seeking of individual consent for flagging under section 60: support for use of patient identifiable information of the Social Care Act 2001 on 07/04/2004. This exemption applies only in England and Wales.

An application to Trent MREC for the case note review has been made in 2005.

6.3 Participant Consent:

6.3.1 Part 1: Flagging

Practices randomised to the intervention arm (ProtecT trial) will be approached and informed consent will be sought from the senior partner for inclusion of the practice. Voluntary individual informed consent for the intervention and for flagging is sought from all men attending prostate check clinics.

Practices randomised to the comparison arm will be approached and informed consent will be sought from the senior partner for inclusion of the practice. Practices that consent will be provided with current information from the NHS prostate cancer risk management programme to advise them of current standard management of prostate cancer.

All GP practices will be asked to put up a poster that will give men the opportunity to opt out of having their records flagged.

The seeking of individual consent for flagging the details of men in the comparison practices or of men in the ProtecT practices who neither opt out nor participate in the ProtecT trial would threaten the viability of the study. The Patient Information Advisory Group (PIAG) has granted the study exemption under section 60 of the Health and Social Care Act 2001 in order to provide the legal basis to do this.

6.3.2 Part 2: Case Note Review

Individual informed consent for case note review will be sought from men who are identified as having had a prostate cancer notification.

If the man has died or having died of a cause potentially related to prostate cancer before we can gain consent for case note review, we wish to seek exemption under section 60 of the Health and Social Care Act 2001 through PIAG to review notes without consent.

7. Study population

7.1 General practice enrolment

All GP practices within the catchments of the nine ProtecT clinical centres will be eligible for recruitment, and all men aged 50 to 69 years registered with GP practices in the ProtecT study catchments will be eligible for inclusion.

7.2 Randomisation

The details of general practices in Primary care trusts (PCTs) in each of the study areas in England are obtained from the respective organisation (local health care co-operatives in Scotland and local health groups in Wales). General practices within these areas are identified on ordinance survey maps and then assigned to contiguous groups of 10-12 practices. A computer program using the statistical package Stata® is used to allocate an equal (or near-equal) number of practices to intervention (ProtecT) and control groups: this stratified randomisation scheme ensures that the number of intervention and control practices is balanced within geographic areas and primary care groups. A statistician not involved in the study performs the randomisation process.

8. Inclusion and exclusion criteria

Inclusion criteria

- All GP practices in the study areas.
- All men age 50-69 years on the date of preparation of the list at the general practice

9. Recruitment of participants

9.1 Recruitment of general practices (CC and SMed)

All Practices will be contacted by the primary care co-ordinator Kerry Avery. The GPs and practice manager will be briefed about the CAP and ProtecT study and an information pack, tailored to the arm of trial to which they have been randomised, will be sent out to each practice. In these information packs the practice will be asked to consent to take part in ProtecT or the comparison arm. For those practices consenting to the ProtecT arm, the ProtecT protocol will follow. For those consenting to the comparison arm, information on prostate cancer risk management programme will follow.

9.2 Recruitment of participants (Protect arm)

The ProtecT protocol gives details of inviting participants to attend the prostate check clinic and subsequent process through the trial. In summary, this involves an initial written invitation, followed by a 30-minute prostate check clinic appointment. At this clinic men receive counselling and detailed information about the implications of PSA testing and subsequent treatment. If they consent, blood is taken for a PSA test which is performed only following the receipt of a further 'cooling-off' consent at least 24-hours later. Men with a raised PSA result (≥3.0ng/ml) are invited to attend the urology department for a further PSA, clinical examination, digital rectal examination (DRE) and trans-rectal ultrasound (TRUS)-guided biopsy. Men found to have advanced disease are treated routinely but followed up within the comprehensive cohort. Re-biopsy is offered immediately to those with high grade prostatic intra-epithelial neoplasia (HGPIN) or negative biopsy and a free/total PSA ratio of <0.12. Men with free/total ratio >0.12 or second negative biopsy are offered repeat PSA testing in 12 months. All men with localised prostate cancer (T1-T2, NX, M0) are invited to participate in the treatment trial comparing active monitoring, radical radiotherapy and radical prostatectomy. If randomisation is not acceptable, a patient-led preference for a treatment option is reached. All men who consent to the ProtecT trial are flagged.

9.2.1 Prospective recruitment of the non responders in the ProtecT practices

The addition of a comparison arm to the ProtecT study means that all other men in the ProtecT practices who have not opted out of the ProtecT study need to be flagged with the NHSCR and local cancer registries.

The Research Assistant will go to the participating GP surgeries and download the name, postcode, date of birth, NHS number and GP practice identification number of all men aged 50-69 years onto the study laptop computer. This list will be saved onto a floppy disk and kept at the practice (this method is detailed in the ProtecT Practices SOP).

The invitation letters will be mailed out as in the ProtecT protocol.

Once the Prostate check clinics (PCC) have finished in the practice, the PCC schedules are returned to Smed for data entry and storage. At this point, all the consent pages of the PCC schedules need to be entered prospectively, in order to identify those men who opt out.

Definition of opt out.

1) Those men who say No to PCC invite, once they have received information about the study.

2) Those men who at the PCC say No to participating in the ProtecT study

3) Those men who say Yes to participating in the ProtecT study, but say No to having their records flagged.

4) Men in the ProtecT practice who have requested to be excluded on seeing the poster displayed in the General Practice.

A list of the name, postcode, date of birth and NHS number will be created for each practice of all men participating in and opting out of the ProtecT study. The Research Assistant will return to the participating GP surgeries and reconcile the two lists (this method is detailed in the ProtecT Practices SOP)**.** The details of men to be flagged will be transferred to Smed to enable flagging to be initiated.

9.2.2 Retrospective recruitment of non-responders in the ProtecT practices

Retrospective flagging: Practices who have been involved with the ProtecT study will be returned to and the poster will be displayed in the practice for three months.

If in these practices the original list of men is available, then the Research Assistant will need to reconcile the original list with the list of men who participated or opted out of the Protect trial.

If the original list of men is not available then the Research Assistant will reconstitute the list of men as near to possible to the time of the creation of the original list. The two lists will then be reconciled.

9.3 Recruitment of participants (Comparison arm)

Using the method detailed in the CAP Practices SOP, the research assistant will approach practices randomised to CAP in order to obtain consent. The research assistant in each centre will visit the consented practice to liase with practice staff, and put up the poster. The practice will be given the CaP download protocol. In order to ensure in each cluster the same calendar period is covered in the ProtecT and CAP practices, the CaP practices will either be asked to produce a list of men in the age range 50-69 years who were at the surgery at a particular point in time or a current list of men. (see Appendix 4 for details).

The research assistant will return to the practice after three months and will exclude any man who has requested not to be flagged on seeing the poster displayed in the General Practice. The name, postcode, date of birth, NHS number and GP practice identification number of all men on this list will be transferred to Smed to enable flagging to be initiated.

10. Flagging of men's details with local cancer registries and NHSCR

The lists obtained from the GP practices will be imported into the admin database. At this point any manipulation needed to standardise the data will be performed. Any duplicates will be identified at this point and dealt with. The information will then be imported into the main template. At this point a unique identifier will be allocated to each of the men to signify the arm of the study they are in, the research centre and the GP practice.

The name, postcode, date of birth, NHS number and unique identifier will then be transferred to the NHS Central Register (NHSCR) and local cancer registries, where they will be flagged.

10.1 Identification of a prostate cancer related event

Surveillance for relevant outcomes will be passive and triggered by the occurrence of deaths or cancer registrations in the flagged group.

Once information about a prostate cancer related event has been received, the following information if available will be entered into the template: Date of prostate cancer registration ; Hospital where diagnosis occurred; Man's consultant; Cause of death (text); Original underlying ICD code; Multiple original ICD code and Stage and grade of tumour.

This information will be anonymised using the unique identifier.

11. The Case Note Review

Men who are identified by the NHSCR or Cancer Registries as having had a prostate cancer diagnosis will be approached for informed consent to review their case notes. As prostate cancer is often slow-growing and not always life-threatening, we need to collect data from case notes for three major purposes:

a) to ensure we determine as accurately as possible the cause of death in men diagnosed with prostate cancer

b) to ensure accurate determination the progression and outcome of prostate cancer

c) to ensure accurate determination of the diagnostic and treatment pathways followed by men for the economic evaluation

11.1 Participant consent procedure

Initially, the man's GP will be contacted and asked to indicate whether the man is alive and currently fit enough to be approached (see **GP letter&consent formV1_15.09.05**. A slightly different letter is sent when a man has moved from a participating practice to a non-participating practice - **GP(other)letter&consent formV1_15.09.05**):

a) if the man has died before we can gain consent for note review, we wish to seek exemption under section 60 of the Health and Social Care Act 2001 through PIAG to review notes without consent

b) men whom the GP indicates are well enough (i.e. not terminally ill or currently temporarily unwell) will be contacted by post by the GP, who will send an invitation letter to the man (on practice headed notepaper, signed by the GP), an information sheet and two copies of a consent form (see **Patient Invitation letter(GP)V1_15.09.05**, **Patient Information sheet(GP)V1_15.09.05** & **Patient Consent form(GP)V1_15.09.05**).

The men will be asked to carefully read the information sheet and complete the consent form. The consent form has been designed to give the man the following options:

i) to agree to take part in the study

ii) to seek like further information about this study, either from a study researcher, or at a face-to-face appointment with the man's GP or the practice nurse. If the man seeks a face-to-face appointment with the GP or practice nurse, face-to-face consent will be obtained from the man at the time of this appointment.

iii) to indicate that he does not wish to participate in the study to access his medical records.

The man will be asked to keep a copy of the consent form and the information sheet for his records. If it is not possible to contact the man via the GP, the treating urologist or oncologist will be asked to request consent (see **Cons letter&consent (ProtecT)V1_15.09.05**, **Cons letter&consent (non-ProtecT)V1_15.09.05, Patient Invitation letter(cons)V1_15.09.05, Patient Information Sheet(cons)V1_15.09.05, Patient Consent form(cons)V1_15.0905)**. Slightly different wording is used depending on whether the consultant is based at a hospital participating in the ProtecT trial or not).

There are second versions of each letter to GPs, consultants, and participants which are sent as reminder letters if we do not receive a response after 3 weeks.

11.2 Data collection once a prostate cancer-related event or death has been identified

The data to be collected are details and dates of: symptoms and signs of prostate cancer presence and progression, diagnostic and monitoring tests, histological grade of cancer, tumour stage, treatments received and outcome, complications of prostate cancer and its treatment, co-morbidities, and other resource use data related to prostate cancer diagnosis and treatment not otherwise covered by the above variables (length of inpatient stay, outpatient appointments). This data will be abstracted onto a standardised proforma by trained research assistants. It will be supplemented by scanned copies of relevant inpatient and outpatient medical records, including in-patient notes in the last 2 months before death, pathology / radiology reports, and copies of discharge and outpatient letters detailing important co-morbidities and evidence of prostate cancer progression / metastases.
These data and scanned documents will be fully anonymised.

11.3 Cause of Death Review

For men in the study who have died of a cause potentially related to prostate cancer, summary vignettes and supporting scanned documentation will be submitted to the Cause of Death (COD) Committee. The aim is that data supplied for the death review should be identical, whether the individual had a screen-detected cancer or not, thus any mention of the ProtecT trial, cancer screening tests, and initial clinical presentation (both screen-detected and symptomatic) will be removed to ensure reviewers are blind as to the allocation in the trial.

In order to ensure comparability of information with the ProtecT trial and to allow accurate ascertainment of cause of death, the same endpoint committee as for the ProtecT trial will be established, chaired by Professor Michael Baum (TSC Chair). They will be blinded to the arm of the trial and will scrutinise death certificates and investigate/confirm the true cause of death. Independent members will be invited to join including representatives from the ERSPC (Professor Fritz Schröder, Rotterdam) and Scandinavian trials (Professor Jan Adolfsson) and PLCO (Peter Albertson, USA), all of whom have already developed relevant proformas and algorithms for ascertainment.

See Appendix 5 for the protocol for cause of death review.

11.4 Data collection 10 years from the initial flagging (in prospective cases) or from the agreed time point (in retrospective cases)

At this point in time research assistants will do a second case note review to obtain information of any further treatment in relation to prostate cancer since the original data collection.

12 Outcome measures

12.1 Primary outcome

Prostate cancer mortality at 10 years

12.2 Secondary Outcomes

- All-cause mortality at 5,10 and 15 years
- Prostate Cancer mortality at 5 and 15 years
- Disease status and staging
- Cost-effectiveness
- Health related Quality of Life

The outcomes will be evaluated in the following way

1. Prostate cancer mortality

Given the problem of ascertainment bias in attributing cause of death,[9] as a consequence of both prostate cancer detection and possibly treatment,[10] an endpoint committee will be established. In order to ensure comparability of information with the ProtecT trial and to allow accurate ascertainment of cause of death, the same endpoint committee as for the ProtecT trial will be used, chaired by Professor Michael Baum (TSC Chair). They will be blinded to the arm of the trial and will scrutinise death certificates and investigate/confirm the true cause of death. Independent members will be invited to join including representatives from the ERSPC (Professor Fritz Schröder, Rotterdam) and Scandinavian trials (Professor Jan Adolfsson) and PLCO (Peter Albertson, USA), all of whom have already developed relevant proformas and algorithms for ascertainment.

2. Disease status and staging

This will be achieved by case-note review when permitted.

3. Cost-effectiveness

A full economic evaluation will be conducted and subject to ethical approval data will be used to develop a probabilistic model (see Appendix 1).

13.Analysis

The primary analysis will be based on those deaths classified as from prostate cancer by the independent panel. Random-effects Poisson regression models (also known as negative-binomial regression models) will be used to estimate rate ratios comparing prostate cancer mortality in intervention and comparison practices, allowing for clustering by including the general practice of each participant as a random effect. These methods will also be used to estimate rate ratios comparing all cause mortality and all cancer mortality in intervention and control practices, and also comparing “probable” or “possible” prostate cancer deaths, should the independent panel decide to classify some deaths in this way. The relatively large number of practices randomised, and the stratified randomisation scheme, should ensure that practices are approximately balanced with respect to prognostic factors such as socio-economic position (using Jarman or Townsend scores) at the time of

randomisation. However, we will conduct sensitivity analyses to confirm that controlling for any imbalances makes little or no difference to the estimated rate ratios comparing intervention and control practices.
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 used the optimal treatment(s). 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 extended study.

Other analysis of interest could include a comparison of underlying rates of prostate cancer in men who do and do not consent to screening. This would be derived by comparing rates in men in intervention practices who do not attend for case-finding with those in control practices, assuming that men in the control practices represent comparable populations of men who would and would not have consented to screening if invited.

14. Economic Evaluation

The economic evaluation will be led by Dr Sian Noble (Smed) and the probabilistic modelling will be led by Dr Jane Wolstenholme. The purpose of the economic evaluation will be to compare the change in costs and change in effects associated with routine screening for prostate cancer, relative to a population in which no routine screening takes place i.e. the status quo from a UK perspective. In essence this will comprise data to be collected on the resource-use, unit costs and utilities related to screen-detection and non-screen detection and the resultant treatment of prostate cancer and its complications (see Appendix 1 section 3.6.1 for details). Subject to ethical approval, data from the ProtecT and ProtecT extension studies will feed into a probabilistic decision-analytic model developed by Wolstenholme and Gray (see Appendix 1 section 3.6.2) which simulates the trial and lifetime costs, effects and cost-effectiveness of screening.

15. Health Related Quality of Life

The HRQL will be co-ordinated by Miss Jane Blazeby. Appendix 2 gives details of the current submission to Cancer Research UK.

16. Data management and security

The study will use whenever possible a dedicated network (NHSnet) to transfer data. RC4 encryption will be used in all data transfers. Within the Department of Social Medicine the database which links the patient personal details (names, postcodes) with the allocated study id will be maintained on a password protected database on a server dedicated solely for the use of this study, and a valid username and password combination will be required to access this information via dedicated terminals. Only senior members of the project team and computer staff will have access to this database. Patient identifiable information will be held on a separate database to any clinical data.

Once the Department receives a possible prostate cancer related event, information necessary to identify the men's hospital records (name, date of birth, postcode, NHS number, consultant's name and study id) will be transferred to the clinical centres. Once the records have been identified, then anonymised clinical data and records will be obtained and transferred back to the Department of Social Medicine. At no point will abstracted information be transferred to Social Medicine with personal details. Abstracted information will always be transferred in an encrypted form, identifiable only through the encrypted ID. The NHSnet will be used whenever possible to transfer abstracted information. Data will be held in a secure area on the Trust's local area network. This area will be restricted to staff employed by the CAP/ProtecT study. The data will be deleted from this area as soon as successful transfer to Social Medicine has been confirmed.

Once at Social Medicine, the abstracted information will be stored in a specific clinical database on a stand-alone secure server, physically separate from the Departmental Network. This server and associated PCs will form their own network, which will be separate from the main Departmental network, and is protected using a

combination of passwords and file permissions. Only the Department's IT staff have authority to manage system security. Staff who are authorised to access this information will not leave their terminal unattended without it being electronically locked. Only for analysis purposes will the anonymised data be transferred to databases held on the Departmental network, and then for a limited time period, in a format only identifiable through the study id.

When transfer via the NHSnet is not possible, encrypted data will be downloaded onto a CD and sent to the Department of Social Medicine using Royal Mail's Special Delivery. Once information has been transferred to the secure server, the CD will be destroyed using a CD cruncher.

Data held in the Department of Social Medicine will conform to the Department Data Security Policy and Department Compliance with the Data Protection Act policies, and according to Department of Health research governance standards.

17. Management and ethical considerations and study organisation

A Trial Steering Committee and a Data Monitoring Committee will oversee the CaP trial. Written records will be taken of each meeting and copies held by the study coordinator.

17.1 Trial Steering Committee (ProtecT and CaP)

- Chair: Professor M Baum (London)
- Dr J Adolfsson (external urologist, Sweden)
- Dr P Albertsen (external urologist, USA)
- Dr D Dearnaley (clinical oncologist/radiotherapist, London)
- Professor M Mason (oncologist, Cardiff)
- Dr M Robinson (uro-pathologist, Newcastle-upon-Tyne)
- Dr A Zeitman (external radiographer, USA)
- ProtecT and CaP Principal investigators (Professors Hamdy, Donovan, Neal, Dr R Martin)
- ProtecT and CaP study senior statisticians (Professor T Peters, Dr J Sterne)
- ProtecT study coordinator (Dr A Lane, Bristol)
- CaP study coordinators (Dr S Noble, Dr C Metcalfe, Bristol)
- ProtecT study senior health economist (Dr L Davies, Manchester)
- ProtecT Coordinating Nurses (Mr P Holding, Sheffield; Ms T Lennon, Newcastle)
- Observers from the NCCHTA

The TSC will meet annually in January.

17.2 CaP Data Monitoring Committee (DMC)

- Chair: Professor Nick Day (Cambridge)
- [TBA]

The DMC will be convened at any point when there are questions covering the ethics in any part of the trial. Recommendations from the DMC regarding the stopping rules for the study will be taken to the TSC for ratification. The DMC will meet annually unless otherwise necessary. A report will be sent to the TSC with the recommendations from each DMSC meeting. The TSC can invite the DMSC Chair or his representative to attend the TSC if deemed appropriate.

17.3 Study Management Committee meetings

All applicants will meet on a regular basis to oversee the project providing expertise as appropriate. Written records will be maintained of these meetings

17.4 Management Executive Committee

- Professors Donovan, Hamdy, Neal, Dr Martin and Dr Sterne comprise the committee
- All publications using CaP data must be approved by the committee prior to submission of the publication
- The committee retains the decision to publish or communicate study results
- The content of all presentations at scientific meetings using CaP data must be notified to the committee prior to presentation
- The details of publications and presentations at scientific conferences should be notified to the study coordinator a copy of the paper sent on publication

17.5 Organisation of study documentation

All clinical centres will have an investigators' Trial Master File, which will include all relevant information and documentation for the trial. This will include the protocol, financial agreements, CVs of all staff involved in the trial, and any correspondence or emails received pertaining to the study. It will be the responsibility of the research assistant at each site to maintain this file.

17.6 Study monitoring

The study will be regularly monitored by the study co-ordinator through reports, visits and examination of the study database. The study is overseen by the TSC.

18. Publications

Annual reports will be produced for Cancer Research UK. Papers will be prepared for publication in general, epidemiological and urological peer-reviewed journals. The findings will also be presented at national and international conferences. The primary analyses will be undertaken when there is average 10-year follow-up (i.e. end of year 13).

Appendix 1:

Economic data collection and analysis, and probabilistic modelling

Co-ordinators: Dr Jane Wolstenholme and Dr Sian Noble

3.6.1 Collection of resource use, unit cost and utility data

Costs

To carry out a full economic assessment, the cost of the resources incurred by those invited for routine screening for prostate cancer needs to be compared to the costs of a similar population without routine screening. The perspective taken will be that of the NHS. Only costs that are perceived to be the main cost drivers will be collected.

Health service costs

i) Routine screening

In the routine screening group all eligible men will incur health service costs associated with the invitation. For men who attend screening, health service costs will be associated with the PSA test, investigations after a positive screen, complications arising from biopsies, the diagnosis after a true positive screen, the symptomatic diagnosis after a false negative screen, treatment for prostate cancer, treatment of complications after the initial treatment and any further treatment on failure of initial treatment. For men who did not attend screening, health service costs will be associated with investigations after a symptomatic referral, complications arising from biopsies, the symptomatic diagnosis, treatment for prostate cancer, treatment of complications after the initial treatment and any further treatment on failure of initial treatment. The detailed sources of data required for the estimation of the costs associated with these activities are provided in Table 1.1.

ProtecT can provide volume information for the invitations for screening for all men in the routine screening arm, and both volume and unit cost information for the following items for men who attended screening:

- PSA testing
- Investigation after a positive screen
- Complications arising from biopsies
- Diagnosis after a true positive screen
- Treatment after a true positive screen for localised prostate cancer
- Complications following treatment for localised prostate cancer.
- Further treatment on failure of initial treatment for localised prostate cancer

Additional data will also need to be collected within the ProtecT extension study on the resource volumes for men who attended screening for the following items (further details are given in Table sd1.1):

- Symptomatic diagnosis
- Treatment for advanced/ symptomatic cancer
- Complications following treatment for advanced/symptomatic cancer
- Subsequent treatment for advanced/symptomatic cancer

For men who did not attend screening it is proposed that health service resource use is obtained in the same way as for men in the comparison arm (see section ii).

ii) Comparison screening

For men in the comparison arm who do not have any ad hoc screening, health service costs will be associated with investigations after a symptomatic referral, complications arising from biopsies, the symptomatic diagnosis, treatment for prostate cancer, treatment of complications after the initial treatment and any further treatment on failure of initial treatment.

For men in the comparison arm who have ad hoc screening, health service costs will be associated with the PSA test, investigations after a positive screen, complications arising from biopsies, the diagnosis after a true positive screen, the symptomatic diagnosis after a false negative screen, treatment for prostate cancer, treatment of complications after the initial treatment and any further treatment on failure of initial treatment.

In order to obtain the volume of activity associated with men who are diagnosed with prostate cancer in the comparison arm and in men who were in the screening arm but did not attend screening, it is proposed that the men are flagged and their clinical notes are obtained once their cancer registration has been identified. Two snapshots of time are proposed for this case note review. Initially after the cancer registration in order to obtain

details of type of referral, pre-diagnosis investigations, biopsy complications, the grade and stage of the cancer and initial treatment. These records would then be re-examined in the last year of follow up research to obtain information on any subsequent treatment for these men (further details are given in Table 1.1).
For most of these items, unit costs will be the same in the ProtecT and extension studies. Where there is reason to believe this may not be the case, revised unit costs will be obtained for the extension study from participating GPs/hospitals, published sources, reference costs and other recognised sources.
Information on the excess number of consultations and investigations arising in men with negative screens in the comparison arm and those in the screened arm who did not attend screening will not be able to be obtained from this note flagging. The following modeling exercise will therefore be used:
The number of men who have cancer after being referred following an ad hoc PSA test will be known.
Information from the ProtecT trial is available on the percentage of men who had a negative PSA test and the percentage of men who had a benign biopsy. Information about the percentage of ad hoc PSA tests which take place in UK general practice is also known.[11] It will be possible using this information to estimate the excess number of investigations for this group by working back from the number of men who have prostate cancer after being referred following a post hoc PSA test.
In relation to obtaining the excess number of investigations in the symptomatic referral group, the number of these referrals will be known. Information about the percentage of benign biopsies from biopsy clinics and the percentage of negative PSA tests from laboratories within the collaborating centres will be used (in addition to information from the ProtecT study in relation to the percentage of negative PSA tests and benign biopsies following screening) to estimate the percentage of negative PSA tests and benign biopsies for symptomatic referrals. Working back from the number of men who have cancer following a symptomatic referral, it will then be possible to obtain the excess number of investigations for this group.

Utility values
Utility values will be obtained using the EuroQol EQ-5D. These data are collected at present from men as part of the existing ProtecT study, at baseline screening, at biopsy for PSA positive men and at 6 months post diagnosis, and annually thereafter for true positive screened men. Utility values can either be assigned directly or inferred from these data, or other studies, with the exception of both biopsy negative and biopsy positive groups. It is proposed that as part of the comparison arm, targeted utility investigations on these groups will be undertaken.

Cost-effectiveness ratios
The data on costs and effects will be incorporated into the probabilistic model, which will provide the framework for the economic evaluation of the ProtecT and extension studies. Cost-effectiveness ratios will be presented in terms of the incremental cost per life year gained and per quality adjusted life year (QALY) gained, based on modelled lifetime costs and effects (see section 3.6.2 below). Future costs and life years will be discounted as recommended for public expenditure by the UK Treasury.[12] [13] Cost-effectiveness results will be presented in the form of cost-effectiveness ratios and acceptability curves. In addition, results will be reported within a net-benefit framework.[14]

3.6.2 Decision analysis

To further inform the economic evaluation and allow the results of the extended ProtecT study to be generalised as widely as possible, a Markov model of screening compared to no screening for prostate cancer, based on a model previously developed by Jane Wolstenholme and Alastair Gray at the University of Oxford, will be further improved and adapted. The existing model represents 12 months WTE researcher time in terms of its development and modification. It currently simulates the costs, effects and cost-effectiveness of screening a cohort of 55 year-old men for prostate cancer, by means of a PSA test every 2 years to the age of 69 and compares this with the status quo. Two Markov models have been constructed, the first simulating the test part of the screening programme, with the second Markov model simulating progression from referral for treatment to death. Outcomes are expressed in life years and quality adjusted life years, and costs in 1999 UK £s discounted to present values. The parameter estimates are currently obtained from the literature and from a group of expert advisers. However one of the limitations of the current model is the lack of UK specific. The ProtecT trial and comparison arm would provide some of the required data for the key parameters in the model (see table 1.2). The current model has shown the key parameters to be uptake rate for screening and the rate of over-diagnosis. These parameters in the current model are from the literature and 'best guess' estimates; the ProtecT and extension studies would provide this much needed data. Of course not all the data required for the model will be provided by the ProtecT studies, and it is hoped that collaborations with other trial centres will be set up so that trial data can be synthesised and important questions investigated thoroughly (e.g. the optimum screening interval). The model is probabilistic, with defined distributions for a range of parameters including pathway probabilities, costs and utilities, and these are used within a Monte Carlo simulation framework.[15]
The current model differs in a number of ways from the proposed trial and will require changes to be made to: the age of the cohort being modelled; the cut-off values for the PSA test; the treatment pathways, and other areas. However, the adaptation of this model and its integration into the extended study plan will serve a number of important purposes. It will enable prioritisation of data collection for the economic analyses; provide a framework within which cost and effect data from the ProtecT studies can be integrated and analysed in a cost-effectiveness analysis (as well as assessing the cost-effectiveness of screening for prostate cancer, it will provide clear answers about the relative cost-effectiveness of treatment pathways for localised cancer cases); provide a means to estimate lifetime costs and effects; provide a robust probabilistic method for handling uncertainty; allow results from the ProtecT studies to be generalised to other care settings and allow other data from parallel and future studies such as the ERSPC and PLCO trials to be incorporated in the analysis. These trials have proposed using a microsimulation model (MISCAN) to assess the cost-effectiveness of prostate cancer screening. The probabilistic Markov model proposed here would differ from the MISCAN model in that:

- it would model a population cohort rather than individuals;
- it would be using UK specific data (for the baseline model) rather than data from other European countries and the US;
- it would provide a transparent and reproducible model undertaken using Microsoft Excel™ software (used widely in the public sector) as an aid to decision makers rather than a specifically developed computer programme.

A recent consensus conference on decision analytic modelling in economic evaluation highlighted the fact that researchers should try to validate their models.[16] An advantage of having both the UK based probabilistic Markov model and the MISCAN model is that the results can be compared and validated.

Table 1.1

Sources of volume and cost data for case-finding and comparison arms

(i) Case-finding arm (screening)

Unit of activity	Source of volume	Source of resource use and cost
1. Invitation	**ProtecT**	The unit cost of an invitation will be obtained from existing screening programmes such as the NHS Breast Screening Programme
2. PSA testing	**Protect** and other screening programes	The time to take a blood sample and the total length of the consultation will be logged for a sample of men in ProtecT. Detailed costing of this procedure including laboratory costs are available from the ProSPECT study.
3. Investigations after a positive screen	**ProtecT**	Type of investigations will be taken from ProtecT data. Associated costs will be obtained from hospital finance departments, urology departments, radiology departments, hospital laboratories, published data sources eg. NHS reference costs.
4. Complications arising from biopsies	**ProtecT**	Type of treatment for complications will be taken from ProtecT data. Costs will be obtained from hospital finance departments, published data sources eg. NHS reference costs.
5. Excess of investigation for symptomatic men with benign diagnoses	Modelling exercise	The unit costs for the investigations will assumed to be the same as in the screened group
6. Diagnosis after a true positive screen	**ProtecT**	The stage and grade of cancer detected, will be taken from ProtecT data. Costs will be obtained from hospital finance departments, published data sources eg. NHS reference costs.
7. Symptomatic diagnosis after a false negative screen or following non attendance for testing	Comparison arm	The stage and grade of cancer detected and their pre diagnosis investigations will be ascertained from the case note review. Unit costs unit costs for the investigations will assumed to be the same as in the screened group.
8. Treatment after true positive screen for localised prostate cancer	**ProtecT**	Type of treatment by stage and grade, will be taken from ProtecT data. Costs will be obtained from hospital finance departments, published data sources eg. NHS reference costs.
9. Treatment after true positive screen for advanced prostate cancer	Comparison arm	Type of treatment by stage and grade will be obtained from the case note review. Costs will be obtained from hospital finance departments, published data sources eg. NHS reference costs.
10. Initial treatment for prostate cancer following a symptomatic diagnosis	Comparison arm	Type of treatment by stage and grade will be obtained from the case note review. Costs will be obtained from hospital finance departments, published data sources eg. NHS reference costs.
11. Complications following treatment of asymptomatic localised prostate cancer	**ProtecT**	Type of treatment for complications, will be taken from ProtecT data. Costs will be obtained from hospital finance departments, published data sources eg. NHS reference costs.

Unit of activity	Source of volume	Source of resource use and cost
12. Complications following asymptomatic advanced prostate cancer	Comparison arm	Type of treatment for complications, will be taken from Case note review. Costs will be obtained from hospital finance departments, published data sources eg. NHS reference costs.
13. Complications following treatment for symptomatic prostate cancer	Comparison arm	Type of treatment for complications, will be taken from ProtecT data/Case note review. Costs will be obtained from hospital finance departments, published data sources eg. NHS reference costs.
14. Further treatment if initial treatment fails	**ProtecT**/ Comparison arm	Type of further treatment, will be taken from ProtecT data/Case note review. Costs will be obtained from hospital finance departments, published data sources eg. NHS reference costs.
15. Primary care monitoring morbidity after diagnosis	**ProtecT**	Type of consultation and medication prescribed will be taken from ProtecT economic evaluation. Practice nurse and GP time and overhead costs will be taken from published sources e.g. PSSRU publication

(ii) Comparison arm

Unit of activity	Source of volume	Source of resource use and cost
1. Excess of investigation and consultation for men with negative screens	Modelling exercise	The unit costs for the investigations will assumed to be the same as in the screened group
2. Investigations of men with a prostate cancer diagnosis	Comparison arm	Type of investigations will be obtained from the case note review. Costs will be assumed to be the same as in the case-finding group
3. Initial treatment for prostate cancer following diagnosis	Comparison arm	Type of treatment will be obtained from the case note review Costs will be assumed to be the same as in the case-finding group
4. Complications following initial treatment	Comparison arm	Type of treatment for complications, will be taken from case note review. Costs will be assumed to be the same as in the case-finding group
5. Further treatment	Comparison arm	Type of further treatment, will be taken from Case note review. Costs will be assumed to be the same as in the case-finding group
6. Primary care monitoring morbidity after diagnosis	**ProtecT**	Number and pattern of consultations per man with prostate cancer (by treatment) will be assumed to be the same as for the *ProtecT* group. Costs will be assumed to be the same as in the case-finding group

Table 1.2

Key additional parameters obtainable from the ProtecT study and trial

a) Parameters currently used in the 'test' component of the decision analytic model

Description of model parameters	**Potential source for empirical data**	
	ProtecT trial	***Comparison arm***
1. Number of validated cases in screen and comparison arm	✓	✓
2. Initial screening attendance rate	✓	
3. Proportion of population with serum PSA > 3ng/mL by age (50-69)	✓	-
4. Continuation rate from positive PSA test to biopsy	✓	-
5. Complication rate from biopsy	✓	-
6. Proportion of patients (screen-detected, refusers, no screen) at clinical stage T1NxM0 by age	✓	✓
7. Proportion of patients (screen-detected, refusers, no screen) at clinical stage T2NxM0 by age	✓	✓
8. Proportion of patients (screen-detected, refusers, no screen) at clinical stage T3-4NxM0 by age	✓	✓
9. Proportion of patients (screen-detected, refusers, no screen) at clinical stage T1-4NxM1 by age	✓	✓
10. Proportion of cases detected post-negative screen by year	-	✓
11. Utilities (EQ-5D) at various stages of the patient pathway	✓	✓
12. Unit cost per invitation to attend, PSA test, ultrasound & biopsy, biopsy complication	✓	-

b) The 'treatment' component of the decision analytic model

Description of model parameters	Potential source for empirical data	
	ProtecT trial	*Comparison arm*
1. Rate of disease progression and subsequent treatment - screen detected	✓*	-
2. Rate of disease progression and subsequent treatment – non-screen detected	-	✓
3. Rate of disease progression and subsequent treatment - refusers		✓
4. Death from prostate cancer (screen, non-screen, refusers)	✓	✓
5. Probability of complications following radical treatment	✓	-
6. Cost of active monitoring	✓	-
7. Cost of radical treatment	✓	-
8. Cost of palliative care	✓*	-
9. Cost of complications	✓	-
10. Utility of active monitoring	✓	-
11. Utility of radical treatment	✓	-
12. Utility of complications	✓	-
13. Utility of palliative care	✓*	-
14. Rate of over-diagnosis	✓	✓
15. Lead time in years	✓	✓

* *Supplemented from the literature*

Appendix 2

Evaluating population-based screening for localised prostate cancer in the United Kingdom: impact on quality of life and men's experiences in the ProtecT study

Co-ordinator: Miss Jane Blazeby.

As indicated above, whilst the primary outcome in this trial is prostate cancer mortality, the possible detrimental effects of screening and subsequent treatment for prostate cancer on physical and psychosocial well-being (health-related quality of life) are relevant secondary outcomes. The impact on health-related quality of life (HRQL) may become critically important if there is no reduction in prostate cancer mortality in the screened group or if the reduction is small. HRQL data will also inform the overall balance between the advantages and disadvantages of prostate cancer screening by providing patient-based outcome data.

3.6.2.1 Current evidence about the impact of screening on HRQL

The ERSPC and PLCO studies include assessment of HRQL using a generic health measure (SF-36), two modules from the UCLA prostate cancer index (urinary and bowel functioning) and a specific sexual functioning scale.[17] Recent publications indicate that HRQL impairment after the screening biopsy is transient and that the screening process itself does not seem to result in appreciable differences between screened subjects and controls.[18] In another non-randomised study HRQL data from patients with screen detected prostate cancer have been compared with data from clinically diagnosed patients.[19] Screen detected tumours were of more favourable stages and grades than clinically diagnosed tumours. Generic SF-36 scores were similar between clinically diagnosed patients and normative population data but were better in the screen detected prostate cancer group. There were no reported differences in sexual function or bowel symptoms between all groups. Urinary symptoms were less severe in screen detected T2/3 cancer group. It appears therefore that HRQL is related both to tumour stage and the detection method. Reasons for better HRQL in the screened group may be because screened men are healthier than the general public or because patients with screen detected lesions have re-evaluated their perceptions of HRQL following a cancer diagnosis. This study emphasises the need for disease specific baseline HRQL data before treatment to evaluate post treatment impact on HRQL.

These preliminary HRQL data from the European/US studies indicate that it is important to study screened subjects and controls. They emphasise that HRQL information from trials in prostate cancer outside screening cannot be extrapolated into screening studies. Although HRQL is being assessed in the European and US studies it is important to address these issues in this proposed extension. It is essential that data collection is extended from the current ProtecT trial to ensure that comparisons can be made with non-screened individuals and populations, as well as to provide data relevant to UK patients.

3.6.2.2 The impact of treatment induced by prostate cancer screening on HRQL

The impact of radical treatment for clinically detected early prostate cancer on HRQL, has been well described.[20] [19] Prostatectomy and radiotherapy differ in the type of HRQL impairment, and data are valuable for informed decision making and treatment choice. The impact of treatment for screen detected prostate cancer, and for active monitoring in particular, is not well described and this is being addressed in the ProtecT trial.

3.6.2.3 HRQL assessment in ProtecT

In the ProtecT trial men who attend study clinics undergo assessment of HRQL with a generic health status questionnaire (SF-12), an anxiety and depression scale (HAD), assessment of basic urinary symptoms (ICS*male*), and a utility measure (EuroQoL). After randomisation and treatment additional tools are used to assess sexual function (ICSsex), more detailed urinary symptoms (ICS*males*SF) and generic and prostate cancer specific HRQL issues (FACT-P). Although the ProtecT trial currently collects a considerable amount of data about the impact of treatment for screen detected prostate cancer on HRQL, there are important

additional issues that need to be addressed within this extension to allow a detailed assessment of the impact of on HRQL.

3.6.2.4 HRQL assessment in proposed extension
The aims of this part of the extension are:

a. To evaluate the impact of screening for prostate cancer on HRQL and anxiety between screened men and controls
b. To compare HRQL (anxiety and physical symptoms) in patients with screen detected cancers to those of clinically diagnosed cancers.
c. To describe the impact of treatment for screen detected prostate cancer on all aspects of HRQL (in the ProtecT trial)

HRQL data will be collected from the following groups of men who are potentially most likely to experience change in HRQL as a result of screening:
Group 1 Men participating in screening (before PSA test). A randomly selected sample will be taken from ProtecT study participants.
Group 2 Men screened negative after PSA result. Questionnaires will be posted to a random sample of men after receipt of their result.
Group 3 Men with PSA false positive results (negative biopsy). Questionnaires will be posted to men after receipt of their result.
Group 4 Men with screen detected cancers (randomised within ProtecT trial). A randomly selected sample will be taken from ProtecT study participants.
Group 5 Men with clinically diagnosed cancers in the control group and in the 'did not attend ProtecT invitation' group. Men identified as incident cases will be posted the study questionnaires with an invitation to participate in a study of quality of life.
In keeping with the other parts of this extension, intervention in the comparison practices will be avoided as much as is possible. Thus, where possible, comparisons will be made with normative data. The exception will be men identified with clinically apparent prostate cancer in both arms of the study who will be identified by cancer registries, and will then be invited to participate in a study of their quality of life.

Data on psychosocial and physical aspects of HRQL will be collected and compared as follows:

Groups of men	Data	Comparisons
1. Before PSA	HAD & SF12 & ICS	Normative data
2. Negative PSA	HAD & SF12	Normative & Group 1
3. False positive	HAD, SF12 & ICS	Group 2 & Group 4
4. True positive	HAD, SF12, ICS & FACT-P	Group 5 & treatment arms of ProtecT
5. Incident cancers in control and 'did not attend' groups	HAD, SF12, ICS scales & FACT-P	Group 4 and Group 3

Sample size calculations are based on changes in the HAD scale scores. Based on analyses of data from the ProtecT feasibility study, we assume that a typical mean HAD score in this population for both anxiety and depression is 5, and that the standard deviation is 3.5. Previous experience with measurement of HRQL in studies where individuals are grouped at GP practice level has shown very little effect of clustering.[21] However, a design effect of 1.5 has been applied to sample size calculations. Assuming a sample size of 380 in each of the relevant comparison groups identified in the Table above, and a 5% significance level, we will have 90% power to detect an increase of 1 in the HAD scale.

3.6.2.5 Justification of selected HRQL measures
The generic health status measure SF-12 has 12-items comparable with the SF-36, yet with the advantage of being easier and quicker to complete.[22] It is reliable, valid and responsive to changes in health status, although unlikely to be applicable to patients who are severely ill or disabled. The twelve items form physical and mental component summary scores. This measure is therefore an ideal screening tool. It will convey information about two of the key quality of life domains (physical and mental function). It is quick and easy to complete. It has been well validated and normative population data are available for comparison.

The Euroqol[23] is a generic health index that produces a utility score between 0 and 1. It may be used to weight life expectancy within a quality adjusted life year. It is easy to complete and provides data that is comparable across populations.

The Hospital Anxiety and Depression scale (HAD) is a widely used tool for assessing psychological distress in patients and non-clinical groups.[24] It consists of 14 items divided into two scales of anxiety and depression. Previous work in patients with early prostate cancer demonstrates that although psychopathology is low overall, some men experience distressing symptoms and this tool is sensitive to these problems.[25]

The Functional Assessment of Cancer Treatment – Prostate (FACT-P)[26] combines a generic cancer tool (FACT-G – 28 items) with a prostate cancer specific module (additional 12 items). Both have been widely tested and demonstrate good content, construct and clinical validity. These questionnaires are most suitable for detecting symptoms of advancing prostate cancer and side effects of treatment, particularly radical therapies. They are currently used in follow-up in the ProtecT trial.

*The International Continence Society urinary symptoms (ICS*male *and ICS*male*SF) and sexual functioning (ICS*sex*) questionnaires are self-completed questionnaires that have been validated for measuring these physical, symptomatic outcomes in middle-aged and elderly men.*[27] [28]

Appendix 3
Sample size estimates

3.11.1 Prostate cancer mortality

Reductions in prostate cancer-mortality of the order of 15-20% are likely to be important to the NHS.[5, 6] On the basis of current national data (England and Wales) on prostate cancer-mortality[1] and incidence[29] a control cohort of 230,000 men aged 50-69 years at recruitment would experience a total of 40,400 deaths, 1,100 prostate cancer deaths and 4,400 incident cases of prostate cancer over 10 years follow-up (2,103,600 man-years). However, in the assessment of cancer screening the appropriate comparison is mortality in the population not known to have disease at the start of the study, as this is the only group that could benefit from early diagnosis through screening.[30] The majority of prostate cancer deaths in the early years of the study, in both control and intervention arms, will occur in individuals diagnosed before the study began. To account for this, the estimates of prostate cancer-mortality in the control arm have been adjusted using the multipliers used in the design of the ERSPC and PLCO studies. The effect of this is to reduce the estimate of prostate cancer deaths in the control arm amongst those without a pre-existing diagnosis of prostate cancer to c.900 over ten years follow-up.

A consequence of randomising at practice level is that the outcome varies less between groups of individuals than between individuals, reducing the effective sample size.[31] The extent of this effect depends on the degree to which events cluster within study populations. Such data are not routinely collected in the UK, so we have relied on a pilot project in County Durham Health Authority in which data on all cause mortality and prostate cancer specific mortality have been collated by GP practice. The between-practice coefficient of variation (standard deviation of the true rates divided by the mean rate) was estimated to be 0.7 for prostate cancer mortality and 0.3 for all-cause mortality. This coefficient of variation for prostate cancer mortality is much higher than expected, and so we present power calculations for a range from 0 to 0.7. For all cause mortality we use a range of 0 to 0.4.

We have used a method proposed by Hayes and Bennett to estimate the power of the proposed study allowing for the clustered design.[32] The number of clusters required is given by:

$$c = 1 + (z_{\alpha/2} + z_{\beta})^2[(\lambda_0 + \lambda_1)/y + k^2(\lambda_0^2 + \lambda_1^2)]/(\lambda_0 - \lambda_1)^2$$

where λ_0 and λ_1 are the rates in the control and intervention groups, y is the person-years in each group and k is the coefficient of variation. For a given number of clusters the normal distribution value corresponding to the power (z_β) can be obtained through a simple rearrangement of this formula. Our calculations are based on 5% significance, and 400 practices and 2.1 million person-years of follow up in the intervention and control groups. To date, 50% of men invited to join the ProtecT trial participate in case-finding, so (assuming no difference in the incidence or outcome of prostate cancer between men who do and do not participate in case finding, and no intervention effect in men who are not screened), the overall disease-specific mortality rate ratio ORR=(0.5×IRR)+0.5, where IRR is the intervention rate ratio (the effect of screening among men who are in fact screened). In other words, the ORR is the effect of the intervention in the whole target population, which is the effect in men actually screened (the IRR) diluted by the less than 100% participation rates. It thus provides the relevant intention-to-treat measure of effectiveness.

Table 1 shows differences in prostate cancer mortality between intervention and control practices that are detectable with 80% power, for coefficients of varation between 0 and 0.7. The clustered design has little impact on power provided that the coefficient of variation is less than about 0.3. Figures 1 and 2 show detectable overall rate ratios and intervention rate ratios respectively, for 80% power (solid lines) and for 50%, 70%, 90% and 95% power.

Table 1. Differences in prostate cancer mortality between intervention and control practices detectable with 80% power.

Coefficient of variation	Overall rate ratio (ORR)	Prostate cancer deaths in control group	Prostate cancer deaths in intervention group	% reduction in prostate cancer deaths	Rate ratio in men participating in case finding (IRR)*
0	0.87	900	785	12.8	0.74
0.1	0.87	900	783	13.0	0.74
0.2	0.87	900	780	13.3	0.73
0.3	0.86	900	776	13.8	0.71
0.4	0.85	900	768	14.7	0.71
0.5	0.84	900	759	15.7	0.69
0.6	0.83	900	750	16.7	0.67
0.7	0.82	900	740	17.8	0.64

Assuming that 50% of men participate in case finding, IRR=(ORR-0.5)/0.5

Figure 1. Detectable overall rate ratio for prostate cancer deaths, according to coefficient of variation and power.

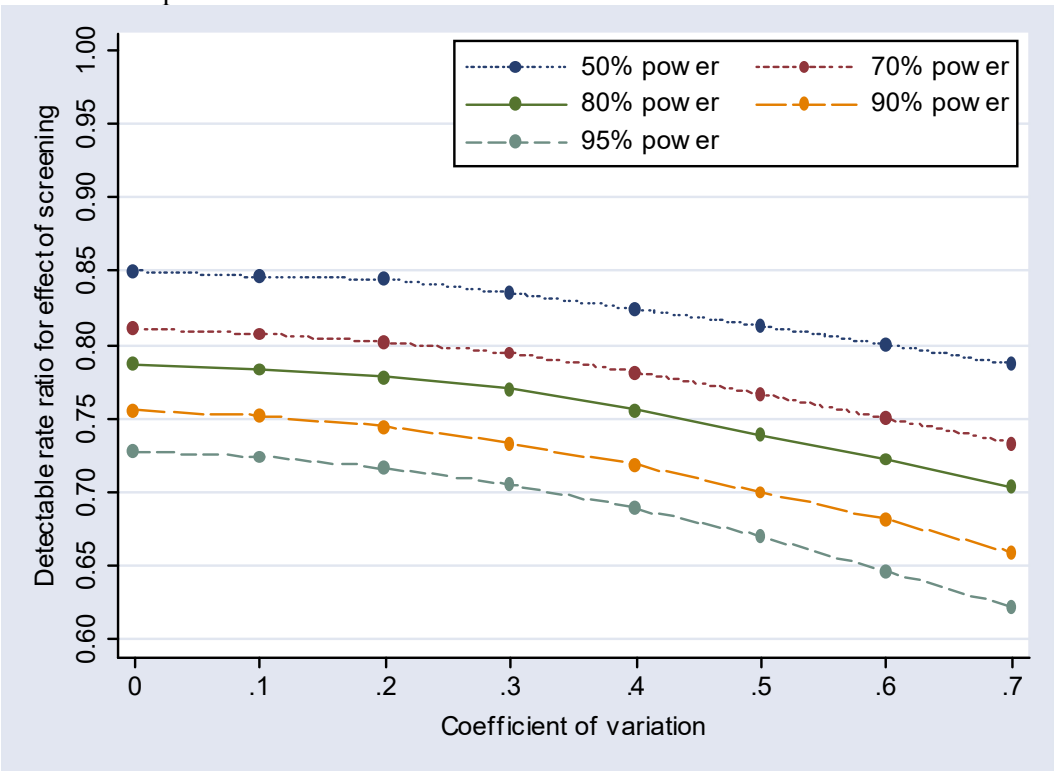
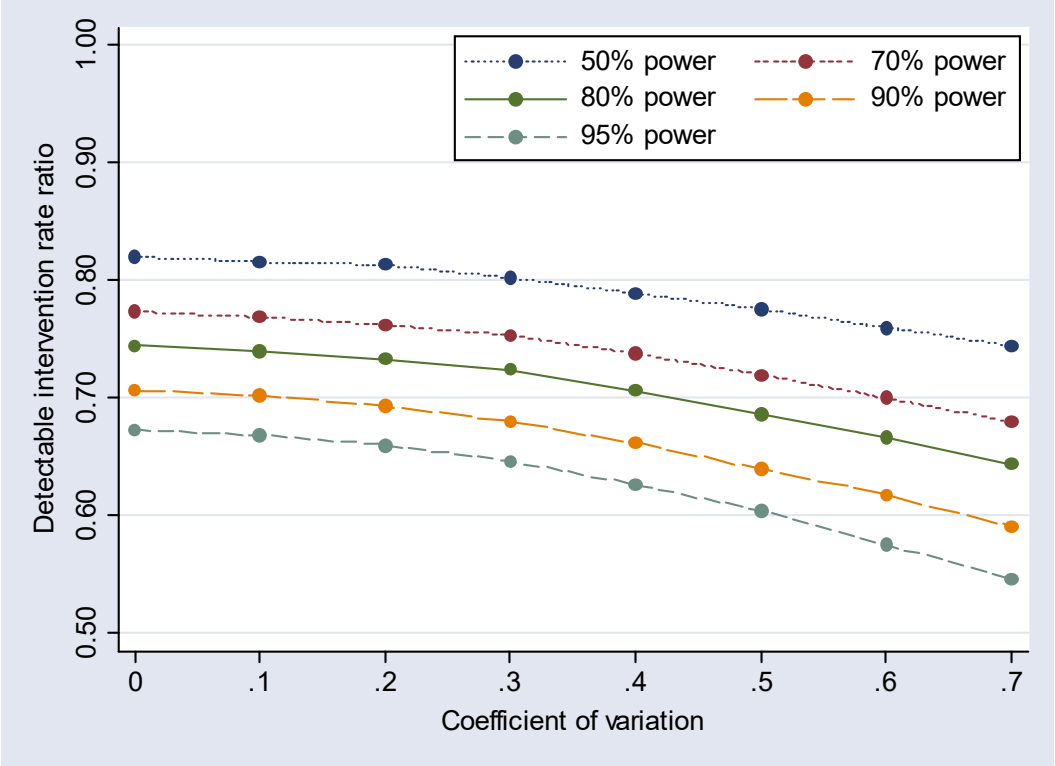


Figure 2. Detectable intervention rate ratio (IRR) for the effect of screening assuming 50% response to invitation to screen, according to coefficient of variation and power.



3.11.2 Contamination

The power of the trial will be reduced if men in the control practices are screened for prostate cancer ("contamination"). A major advantage of this cluster-randomised design is that contamination will be a much less severe problem than would be the case if men were individually randomised and hence were alerted to the possibility of being screened for prostate cancer. Current estimates for contamination in the ERSPC are between 10-40%.[33] Further, the research question is whether the addition of a national prostate cancer screening programme to the unsystematic use of PSA testing will prove cost effective. The level of prior tests can be expected to be the same in the intervention and the control arms, and this is the background against which any new programme will have to demonstrate its effectiveness. Melia and Moss conducted a survey of the use of PSA testing among men aged 45 years and over with no prior history of prostate cancer or radical prostatectomy registered with the MediPlus database (120 computerised practices using the same computer system in various parts of the UK).[34] Within the age-group relevant for the ProtecT study, they reported that 2.1% of men aged 45-69 had received a PSA test in 1999. In men over 45 years, 3.5% had received PSA tests. In the ProtecT trial, men are asked to report previous PSA tests. From 13,228 prostate check clinic attenders on whom data are available, 1,190 reported a previous PSA test (9%). Of the 894 who indicated why they had had this test, 215 (24%) believed this was for urinary symptoms, 407 (46%) because of GP request, 163 (18%) for screening, and 72 (8%) as part of private insurance checks. Practices recruited to the ProtecT trial in the feasibility phase contained more individuals from social classes I and II than the general population, and there was a significant positive correlation between the proportion reporting a previous PSA test and the proportion in social classes I and II (r=0.55, p=0.02). Levels of lower urinary tract symptoms amongst ProtecT trial participants were consistent with levels found in population samples of the same age. Taking all these factors into account, it would seem likely that the underlying rate of asymptomatic PSA testing in this age-group is low. If 25% of tests are undertaken for symptoms, a high estimate of the rate amongst this higher social class than average population would therefore be approximately 7%, and a low estimate would be 2%. This level is confirmed in a check of a computerised non-ProtecT practice in Bristol with a primarily middle-class population: of 851 men aged 50-69 years, 54 without prostate cancer (6%) had ever had a PSA test.

We have estimated the power of the trial, adjusting for contamination rates of 5%, 10% or 20%. Our calculations assume that the the intervention rate ratio applies equally to men screened voluntarily (contamination) and to men screened through ProtecT case finding, that in the intervention practices the proportion of men who respond to case finding is 50%, and that the proportion of men screened voluntarily is the same among those who do and do not respond to case-finding. Table 2 shows differences in prostate cancer mortality that are detectable with 80% power, according to contamination rate and coefficient of variation. Note that the number of prostate cancer deaths in the control group (assumed to be 900 in the absence of any intervention effect) decreases with increasing contamination.

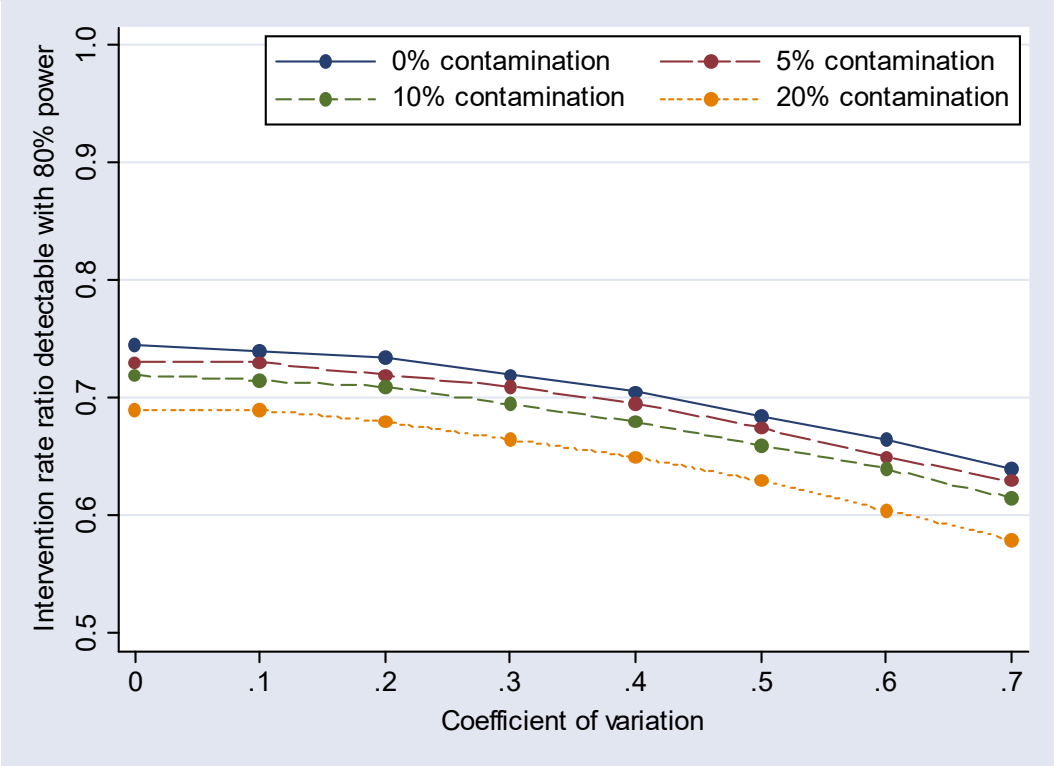
Table 2. Differences in prostate cancer mortality between intervention and control practices detectable with 80% power, assuming 5%, 10% or 20% contamination rates and with different coefficients of variation.

Coefficient of variation	Overall rate ratio (ORR)	Prostate cancer deaths in control group	Prostate cancer deaths in intervention group	% reduction in prostate cancer deaths	Rate ratio in men participating in case finding (IRR)*
5% contamination					
0	0.87	888	772	13.1	0.73
0.1	0.87	888	772	13.1	0.73
0.2	0.87	887	768	13.4	0.72
0.3	0.86	887	763	14.0	0.71
0.4	0.85	886	756	14.7	0.69
0.5	0.84	885	746	15.7	0.68
0.6	0.83	884	735	16.9	0.65
0.7	0.82	883	725	17.9	0.63
10% contamination					
0	0.87	875	761	13.0	0.72
0.1	0.87	874	759	13.2	0.71
0.2	0.86	874	756	13.5	0.71
0.3	0.86	873	749	14.2	0.69
0.4	0.85	871	742	14.8	0.68
0.5	0.84	869	732	15.8	0.66
0.6	0.83	868	722	16.8	0.64
0.7	0.82	865	709	18.0	0.62
20% contamination					
0	0.87	844	733	13.2	0.69
0.1	0.87	844	733	13.2	0.69
0.2	0.86	842	727	13.7	0.68
0.3	0.86	840	719	14.4	0.67
0.4	0.85	837	711	15.1	0.65
0.5	0.84	833	700	16.0	0.63
0.6	0.83	829	687	17.1	0.61
0.7	0.82	824	673	18.3	0.58

* Assuming that 50% of men participate in case finding

Figure 3 displays the intervention rate ratios detectable with different levels of contamination at 80% power, according to the coefficient of variation. The expected 5% contamination level has little effect on power, which is notably decreased only when contamination levels exceed 10%. The solid line corresponding to no contamination is identical to that for 80% power in Figure 2.

Figure 3. Intervention rate ratios detectable with different levels of contamination at 80% power, according to the coefficient of variation.



3.11.3 All cause mortality

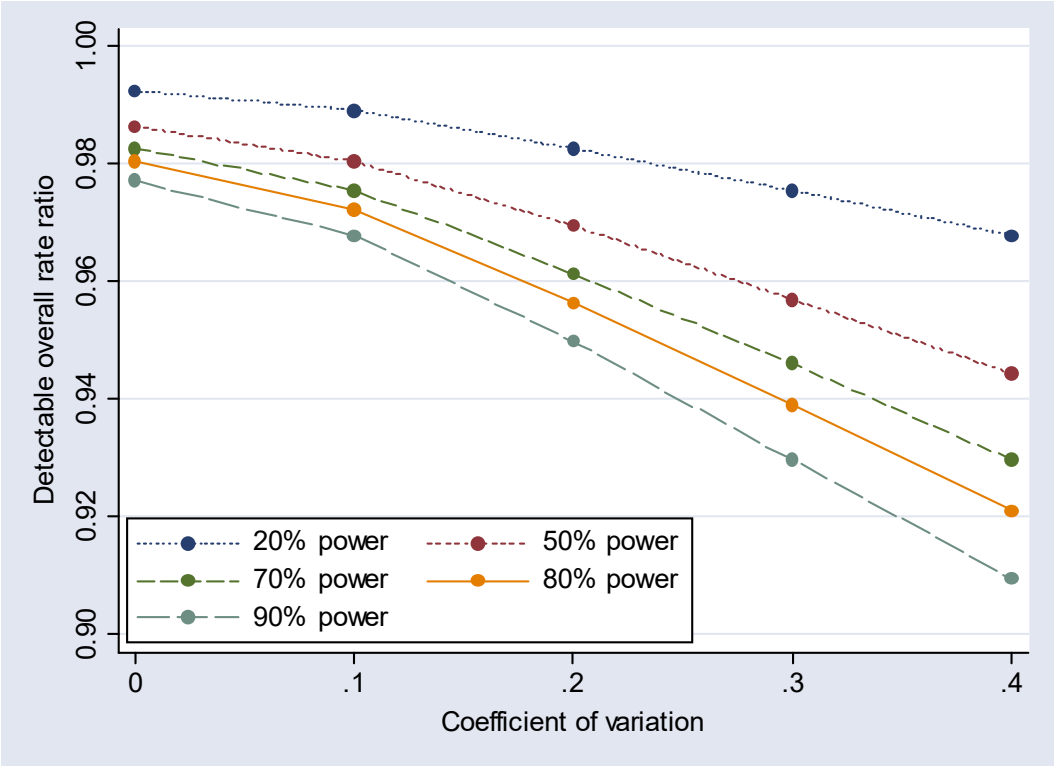
We estimate that a total of 40,400 deaths will occur among men in the comparison practices. Table 3 shows the effects on all cause mortality that can be detected with 50% and 80% power, according to coefficient of variation. Note that the coefficient of variation has a substantial impact on power, because of the large number of events in each practice. The study will have low power to detect differences of the magnitude that might reasonably be expected to occur. The anticipated sample size from ongoing screening trials (ERSPC and PLCO) is 250,000,[35] and pooling those data with data from the proposed study would effectively double this number, giving a total that would approach sufficient power to detect a 1% difference (5% reduction) in all-cause mortality. Figure 4 shows detectable overall rate ratios for all cause mortality at 20%, 50%, 70%, 80% and 90% power, according to coefficient of variation.

Table 3. Effects on all cause mortality that are detectable with 50% and 80% power, according to coefficient of variation.

Coefficient of variation	Overall rate ratio (ORR)	Total deaths in control group	Total deaths in intervention group	% reduction in all-cause mortality	Rate ratio in men participating in case finding (IRR)*
50% power					
0	0.986	40400	39850	1.4	0.973
0.1	0.980	40400	39608	2.0	0.961
0.2	0.970	40400	39168	3.0	0.939
0.3	0.957	40400	38662	4.3	0.914
0.4	0.944	40400	38156	5.6	0.889
80% power					
0	0.980	40400	39608	2.0	0.961
0.1	0.972	40400	39278	2.8	0.944
0.2	0.956	40400	38640	4.4	0.913
0.3	0.939	40400	37936	6.1	0.878
0.4	0.921	40400	37210	7.9	0.842

* Assuming that 50% of men participate in case finding, IRR=(ORR-0.5)/0.5

Figure 4. Detectable overall rate ratios for all cause mortality, according to coefficient of variation.



Taking into account estimates of prostate cancer mortality and the effect of clustering of events within practices, a comparison population of 230,000 men drawn from approximately 400 practices will provide adequate power to detect a policy-relevant detection in disease-specific mortality. To our knowledge, no existing UK cancer screening programme has been introduced or piloted on the basis of evidence from RCTs demonstrating a difference in overall mortality.[8 36] The proposed extension will provide a precise estimate of the effect of a single screening round on prostate cancer mortality and an unbiased estimate of its effect on all cause mortality which will provide minimum and maximum plausible effects, and the opportunity to pool data with other trials.

Appendix 4

Procedure for obtaining GP lists

Background

The aim of this procedure is to ensure that the same calendar period is covered by follow-up of the **ProtecT** and **CAP** practices in each cluster.

It is assumed that statistical analysis of the resulting data will be by a method which explicitly incorporates any changing incidence over time. Event time analysis using Cox's proportional hazards regression would be one way of achieving this. For such analyses it is sufficient that follow-up in the groups to be compared is over the same time period, with no need for a balance in person-years of follow-up during the different calendar periods between the two studies.

The procedure

[1] For a given cluster note the earliest date (referred to below as date E) during which a practice list was obtained for a **ProtecT** practice.

[2] If no lists have been obtained for **ProtecT** practices, or no list was obtained more than 6 months ago, obtain the current practice lists for **CAP** practices in that cluster.

[3] If, for **ProtecT** practices in the cluster, one or more lists were obtained more than 6 months ago, then attempt to obtain a retrospective list for each **CAP** practice consenting to take part until two retrospective practice lists have been obtained for date E.

- Retrospective lists should be obtained for date E if possible.

- If two or more **CAP** practices in a cluster are awaiting the retrieval of their lists then the order in which they are approached must be randomised. Contact Chris Metcalfe for a randomised order.

- If, for a practice, a retrospective list can only be obtained for a date more recent than date E, then obtain a retrospective list for that more recent date. This practice does not contribute to the target of two retrospective practice lists for date E.

- If a retrospective list cannot be obtained at all, obtain the current practice list.

Once two retrospective lists for date E have been obtained, then obtain current practice lists for subsequently consenting **CAP** practices in the cluster. There is no longer a need to randomise the order of approaching practices for that cluster.

Footnote

Where the date of having obtained a list from a **ProtecT** practice is not available, then estimate from the dates at which men were invited to attend for PSA testing.

Appendix 5

Protocol for reviewing causes of death in the CAP & ProtecT trials by the Cause of Death committee

1. CONTENTS

- All participants in the trial who had an incident prostate cancer diagnosed and all deaths notified to the trial co-ordinating centre as being due to prostate cancer will be subject to review by the Cause of Death committee.
- This document outlines
    - deaths that are to be reviewed by the Cause of Death committee
    - procedures for obtaining, anonymising and blinding data
    - the process to evaluate the cause of death
    - the actions following the Cause of Death committee review.

2. OVERVIEW

The following steps are an overview of the process. The Department of Social Medicine will be responsible for managing data extraction, the submission of data to the COD committee, and the collation and entering of the results. More detailed information is provided in the accompanying appendices.

Step 1. Notification of cause of death and selection of deaths for review:

- We will be notified of the fact of death by the Office for National Statistics (ONS).
- All death certificates will be reviewed by an epidemiologist or clinician who will arrange for detailed case note review of any death satisfying any one of the criteria set out in **Appendix A.** These criteria have been adapted from those used by the PLCO Screening Trial[1]. All other deaths will be accepted as certified without review.

Step 2: Case note review

- Details of the treating hospital and clinician notified by the cancer registry will be used to find and retrieve the hospital notes.
- Specifically trained research assistants **blinded to cause of death information on the death certificate** will abstract data from hospital records onto a specially designed standardised proforma. The aim is that data supplied for the death review should be identical, whether the individual had a screen-detected cancer or not.
- This standardised proforma will be supplemented by scanned copies of relevant inpatient and outpatient medical records including in-patient notes in the last 2 months before death, pathology \ radiology reports, and copies of discharge and outpatient letters detailing important co-morbidities and evidence of prostate cancer progression / metastases.
- Clinical records will be edited by the RAs and checked by a reviewer at the Dept of Social Medicine to remove mention of the ProtecT trial, cancer screening tests, and initial clinical presentation (both screen-detected and symptomatic) to ensure reviewers are blind as to the allocation in the trial.

Step 3: Submitting data to the cause of death committee

- Before submitting data to the COD committee, a sessional clinical research fellow will evaluate the adequacy of the information collected for the review. Research Assistants may be asked to revisit the man's notes to obtain any additional information.
- The clinical research fellow will then write a 1 page structured vignette **(Appendix B)** on each man.
- The information submitted to members of the cause of death committee will be: i) the structured vignette; ii) a cause of death committee questionnaire on which the final

underlying cause of death is recorded together with a structured section on which brief reasons for the final decision are recorded **(Appendix C)**.

Step 4: Method of working of the Cause of Death (COD) Committee

- There will be 3 teams of 3 reviewers who are members of the Cause of Death (COD) Committee **(Appendix D: composition of reviewing teams).** The 3 teams will share the workload, each reviewing their own sets of vignettes. The teams will only combine to review difficult cases (see below).
- The reviewers will be asked to review the vignettes (and any additional relevant material considered essential by the research fellow) for evidence of progressive metastases, progressive local recurrence, intervention-related (screening, diagnosis, treatment or follow-up) mortality and serious co-morbidity. There will be a hierarchy of causes of death to choose from **(see Appendix C for detailed definitions):**
    - Definite prostate cancer death
    - Probable prostate cancer death
    - Possible prostate cancer death
    - Intervention-related death
    - Unlikely prostate cancer death +/- prostate cancer a contributory factor
    - Definitely not prostate cancer death
- If all 3 members reach the same conclusion, that conclusion is accepted.
- If there is a disagreement then the 3 reviewers arrange a telephone conference to discuss the case and attempt to reach a unanimous decision. At this stage the reviewers might ask for additional information. Research Assistants will attempt collection of any additional information requested by a COD member.
- Where there are disagreements, a decision-based algorithm will be followed in an attempt to standardise the decision making process (**see paper by Harry de Koning[2])**.
- If disagreements persist, the case is taken to a teleconference review (every 6-12 months) of difficult cases by the whole committee.

Step 5: Actions following death committee review

- Questionnaires are returned by e-mail to the Department of Social Medicine for review and incorporation into the master database.
- Data entry will be blind to the arm of the trial the participant is in.

References

1. Miller AB, Yurgalevitch S, Weissfeld L. Death review process in the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial. Controlled Clinical Trials 2000;21(6, Supplement 1):400S-6S.

2. De Koning HJ, Blom J, Merkelbach JW, Raaijmakers R, Verhaegen H, van Vliet P et al. Determining the cause of death in randomized screening trial(s) for prostate cancer. BJU Int 2003;92(s2):71-8.

Appendix A: Deaths to be reviewed

1. A death certificate diagnosis (from an immediate, underlying, or contributing cause-of-death field) that specifies cancer of the prostate, lung, colon-rectum, or ovary:

ICD-9 185	malignant neoplasm of prostate
ICD-9 233.4	carcinoma in situ of prostate
ICD-10 C61	malignant neoplasm of prostate
ICD-10 D075	carcinoma in situ of prostate

2. A death certificate diagnosis (from an immediate, underlying, or contributing cause-of-death field) that suggests a possible misclassified secondary bone cancer:

ICD-9 170	malignant neoplasm of bone and articular cartilage
ICD-10 40,41	malignant neoplasm of bone and articular cartilage

3. A death certificate diagnoses (from an immediate underlying, or contributing cause-of-death field) that suggests uncertainty of the diagnosis of cancer, such that cancer of the prostate, cannot be excluded, or a metastatic cancer with unknown primary:

ICD-9 187.9	malignant neoplasm of male genital organ, site unspecified
ICD-9 195.2, 195.3	malignant neoplasm other ill-defined sites, abdomen or pelvis
ICD-9 196-199	secondary & unspecified malignant neoplasm
ICD-9 223.9	neoplasm, site unspecified
ICD-9 233.6	carcinoma in situ of genitourinary system, male genital organs
ICD-9 233.9	carcinoma in situ of genitourinary system, urinary organs
ICD-9 236.5	neoplasm of uncertain behaviour, prostate
ICD-9 236.6	neoplasm of uncertain behaviour, unspecified male genital organs
ICD-9 236.9	neoplasm of uncertain behaviour, unspecified urinary organs
ICD-9 239	neoplasm of unspecified nature
ICD-10 C795	secondary malignant neoplasm of bone & bone marrow
ICD-10 C40	neoplasm of uncertain, unknown behaviour, male genital organs
ICD-10 C41	neoplasm of uncertain, unknown behaviour, urinary organs
ICD-10 C80	carcinomatosis
ICD-10 D480	neoplasm of uncertain or unknown behaviour of bone
ICD-10 D487	neoplasm of uncertain or unknown behaviour
ICD-10 D489	neoplasm of uncertain or unknown behaviour, unspecified

4. A death certificate coded to an unknown underlying cause of death:

ICD-9 789	sudden death, cause unknown
ICD-9 797	senility without mention of psychosis
ICD-9 799	other ill-defined and unknown causes
ICD-10 R96	other sudden death, cause unknown
ICD-10 R54	senility
ICD-10 R69	unknown, unspecified cause of morbidity

5. Death from any cause previously notified by the ONS / cancer registry with an incident prostate cancer:

ICD-9 185	malignant neoplasm of prostate
ICD-9 233.4	carcinoma in situ of prostate
ICD-10 C61	malignant neoplasm of prostate
ICD-10 D075	carcinoma in situ of prostate

6. Death from any cause if primarily notified by the ONS / cancer registry with a primary malignancy possibly representing misclassified or metastatic cancer of the prostate. Entry of any one of the following ICD-9/10 codes will trigger death review:

ICD-9 187.9	malignant neoplasm of male genital organ, site unspecified
ICD-9 195.2, 195.3	malignant neoplasm other ill-defined sites, abdomen or pelvis
ICD-9 196-199	secondary & unspecified malignant neoplasm
ICD-9 223.9	neoplasm, site unspecified
ICD-9 233.6	carcinoma in situ of genitourinary system, male genital organs
ICD-9 233.9	carcinoma in situ of genitourinary system, urinary organs
ICD-9 236.5	neoplasm of uncertain behaviour, prostate
ICD-9 236.6	neoplasm of uncertain behaviour, unspecified genital organs
ICD-9 236.9	neoplasm of uncertain behaviour, unspecified urinary organs
ICD-9 239	neoplasm of unspecified nature
ICD-10 C795	secondary malignant neoplasm of bone & bone marrow
ICD-10 C40	neoplasm of uncertain, unknown behaviour, male genital organs
ICD-10 C41	neoplasm of uncertain, unknown behaviour, urinary organs
ICD-10 D480	neoplasm of uncertain or unknown behaviour of bone
ICD-10 D487	neoplasm of uncertain or unknown behaviour of other sites
ICD-10 D489	neoplasm of uncertain or unknown behaviour, unspecified

Appendix B: Structured vignette

Patient ID	
Date of birth	
Date of diagnosis	
Date of death	
Age at death (years)	
Symptoms at diagnosis	
Presence of symptoms/signs of prostate cancer metastases at diagnosis	
Prostate cancer stage at diagnosis	
Prostate cancer grade at diagnosis Degree of differentiation Perineural/vascular spread	
Pathological stage and grade	
Co-morbidity at diagnosis with dates	
Other primary cancers; metastases present (Y/N) & sources of evidence of mets	
Treatments received with dates	
Serial PSA levels with dates (ng/ml)	
Radiology results with dates	
Indications / complications of PC progression since diagnosis with event dates and source of evidence	
Complications of diagnosis and/or treatment with dates	
Hospital admissions with dates	
Date of recurrence following radical surgery or radiotherapy	
Clinical care in last 3 months (e.g. hospice admissions)	
Presence or absence of weight loss or cachexia during the last 3 months of life.	
Date of last consultation	
Last prostate cancer stage before death with date	
Additional notes available (location)	
Additional comments (to be completed by initial medical reviewer)	

Appendix C: Cause-of-death questionnaire

Qu 1: Cause of death - tick one box only:

Cause of death	Yes
a) Definite prostate cancer death	☐ 1
b) Probable prostate cancer death	☐ 2
c) Possible prostate cancer death	☐ 3
d) Definitely intervention-related death	☐ 4
e) Unlikely prostate cancer death	☐ 5
f) Unlikely prostate cancer death but prostate cancer a contributory factor	☐ 6
g) Definitely not prostate cancer death	☐ 7

Definitions

a) Definite *prostate cancer deaths are cases in which there is no doubt that progressive local disease or distant metastases from prostate cancer were the underlying cause of death (e.g. evidence from post mortem, or where no other co-morbidities are possible explanation).*

b) Probable *deaths from prostate cancer are cases in which there was progressive local disease or distant metastases from prostate cancer, but in which there is doubt about whether these were the final direct cause of death, and thus no other clear cause is present(e.g. no other potential cause identified but uncertainty about prostate cancer as a cause exists, or other co-morbidities present but not linked to terminal event). This may also be the case when information is missing about the last years of a patient's life.*

c) Possible *deaths from prostate cancer are:*

- *Cases with progressive local disease (but no progressive cancer metastases) for which there is doubt about whether these were the direct cause of death;*
- *Cases with progressive metastases but origin unknown that caused death or when there is doubt whether these caused death.*

d) Definite intervention-related *deaths arise if some aspect of screening, diagnosis (eg biopsy), treatment or its follow-up are the cause of death. However, to diagnose a screening-related death that had not occurred directly as part of the diagnostic or treatment process would require the reviewers to be unblinded as to the screening status of the man. This requires some thought. An example of the dilemma in the ERSPC trial was a man given radiotherapy for a screen detected prostate cancer who was then found to have bladder cancer. The radiotherapy to his prostate had taken him over the pelvic dose so he could not receive radiotherapy for his bladder cancer, from which he subsequently died.*

e) *"**Unlikely prostate cancer**" deaths arise when distant metastases or local progression are present but are not the underlying cause of death.*

f) Unlikely prostate cancer death but prostate cancer a contributory factor: *It is possible that prostate cancer did not directly result in the patient's death, but was a contributory factor e.g. when distant metastases or local progression are present but are not the direct underlying cause of death. A patient who has a fatal heart attack 2-3 months before they probably would have died from prostate cancer. This would be an unlikely prostate cancer death, but prostate cancer could have been a contributory cause.*

g) "Definitely not prostate cancer" *death occurs when there is no evidence of distant metastases, local progression or other complications of diagnosis or treatment.*

On what evidence was your assessment of the cause of death based:

Q2a: If definite, probable or possible prostate cancer death, on what evidence is this assessment based:

	2i) Tick all that apply	**2ii) Briefly describe the evidence and where this is recorded (e.g. consultant letters, radiological reports, handwritten medical notes)**
Clinical picture[1]	☐1	
High, increasing PSA levels[2]	☐2	
X-ray evidence of metastases[3]	☐3	
Scan evidence of metastases[4]	☐4	
Evidence based on the treatments received[5]	☐5	
Evidence based on pathology[6]	☐6	

[1]*Symptoms or impairments such as anaemia, renal impairment caused by ureteric obstruction, tumour mass leading to gastrointestinal or biliary obstruction, and in hormone relapsed disease: severe LUTS, retention, or incontinence.*
[2]*e.g. Rising PSA after complete tumour suppression / hormonal ablation where PSA rises above 50 ng/ml; rising PSA after radical prostatectomy; PSA above PSA threshold from ProtecT model in men on active monitoring. The sole presence of high or increasing PSA levels should never be assumed to indicate metastases unless other unequivocal evidence is present (see the other five items).*
[3]*Enlarged nodes on CT should be assumed metastatic only if in association with progressive increase in size, regression after hormonal treatment or increasing PSA levels.*

[4]*A few single 'hot spots' on bone scans should be assumed metastatic only if in association with unequivocal evidence on CT, or regression after hormonal treatment.*
[5]*e.g. chemotherapy for hormone resistant disease*
[6]*In subjects who have other invasive carcinomas, histological evidence of cancer type at metastatic site important.*

Q2b: If probable or possible prostate cancer death, what other potential causes of death were there?

_____

Q3: If Definitely intervention-related death,

	Yes	**No**
Q3a: Were complications of treatment the cause of death?	☐1	☐2

	Yes	**No**
Q3b: Were complications of screening / biopsy the cause of death?	☐1	☐2

Q3c: Briefly describe the evidence and where this is recorded (e.g. consultant letters, autopsy reports, handwritten medical notes)

_____

_____

_____

Q4: If Unlikely or definitely not prostate cancer death, what was the most likely cause of death?

_____

Q5: If unlikely prostate cancer death, but prostate cancer was a contributory factor, describe how prostate cancer contributed to the death

_____

_____

_____

_____

Appendix D: Composition of reviewing teams

Chair: to be determined – external chair preferred

Team 1:

Michael Baum
Mary Robinson
Anthony Zeitman

Team 2:

Jan Adolfsson
Pathologist/ epidemiologist/GP
Oncology/health care elderly

Team 3:

Peter Albertsen
David Jewell
Oncology/health care elderly

19. Reference List

[1] 1999 Mortality Statistics, cause. England and Wales (Series DH2 no.26). London: The Stationery Office, 2000.
[2] Homberg L, Bill-Axelson A, Helgesen F et al. A randomised trial comparing radical prostatectomy with watchful waiting in early prostate cancer. NEJM 2002; 347 (11): 781-789.
[3] Lu-Yao G, Albertsen PC, Barry MJ et al. Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality. BMJ 2002; 325: 740.
[4] Frankel S, Davey Smith G, Donovan J, Neal D. Screening for prostate cancer. The Lancet 2003;361:1122-28.
[5] Auvinen A, Rietbergen JB, Denis LJ, Schroder FH, Prorok, PC. Prospective evaluation plan for randomised trials of prostate cancer screening. J Medical Screening 1996;3:97-104.
[6] Gohagan JK, Prorok PC, Kramer BS, Cornett JE. Prostate cancer screening in the PLCO screening trial. Journal of Urology 1994;152:1905-1909.
[7] de Koning HJ, Auvinen A, Berenguer Sanchez A, et al. Large-scale randomized prostate cancer screening trials. In J Cancer 2002;97:237-44.
[8] Olsen O, Gotzsche PC. Cochrane review on screening for breast cancer with mammography. Lancet 2001;358:1340-1342.
[9] Albertsen P. When is a death from prostate cancer not a death from prostate cancer? Journal of the National Cancer Institute 2000;92:590-591.
[10] Newschaffer CJ, Otani K, McDonald MK, Penberthy LT. Causes of death in elderly prostate cancer patients in a comparison non-prostate cancer cohort. JNCI 2000;92:613-621.
[11] Melia J, Moss S. Survey of the rate of PSA testing in general practice. B J Cancer 2001; 85(5): 656-657.
[12] HM Treasury. Economic appraisal in central government: a technical guide for government departments. London: HM Treasury, 1991.
[13] Department of Health. Policy appraisal and health. A guide from the Department of Health. London: Department of Health, 1995.
[14] Fenwick, E, Claxton, K, Sculpher, M, and Briggs, A. Improving the efficiency and relevance of health technology assessment: The role of iterative decision analytic modelling. Discussion Paper 179. York: The University of York, 2000.
[15] Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. Medical Decision Making 1985;5 :157-177.
[16] McCabe, C, and Dixon, S. Testing the validity of cost-effectiveness models. Pharmacoeconomics 2000;17(5):501-513.
[17] Miller AB, Madalinska JB, Church T et al. Health-related quality of life and cost-effectiveness studies in the ERSPC and PLCO. European Journal of Cancer 2001; 37: 2154-2160
[18] Essink-Bot ML, de Koning HJ, Nijs HG, Kirkels WJ, van der Maas PJ, Schroder FH. Short-term effects of population-based screening for prostate cancer on health-related quality of life. J Natl Cancer Inst 1998;90:925-931.
[19] Madalinska JB, Essink-Bot ML, de Koning HJ, Kirkels WJ, van der Maas PJ, Schroder FH. Health-related quality of life in patients with screen-detected versus clinically diagnosed prostate cancer preceding primary treatment. Prostate 2001;46:87-97.
[20] Steineck G, Helgesen F, Adolfsson J, et al. Quality of life after radical prostatectomy or watchful waiting. N.Engl.J Med. 2002;347:790-796.
[21] Clustered randomised trial of an intervention to improve the management of asthma: Greenwich asthma study. U N Premaratne, J A C Sterne, G B Marks, J R Webb, H Azima, and P G J Burney. BMJ 1999; 318: 1251-1255.
[22] Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey - Construction of scales and preliminary tests of reliability and validity. Medical Care 1996;34:220-233.
[23] The EuroQol Group. EuroQol* - a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.
[24] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavia 1983;67:361-370.
[25] Bisson JI, Chubb HL, Bennett S, Mason M, Jones D, Kynaston H. The prevalence and predictors of psychological distress in patients with early localized prostate cancer. BJU.Int. 2002;90:56-61.
[26] Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology 1997;50:920-928.

[27] Donovan JL, Abrams P, Peters TJ. The psychometric validity and reliability of the ICSmale questionnaire. British Journal of Urology 1996;77:554-562.
[28] Donovan JL, Peters TJ, Abrams P, Brookes ST, de al Rosette JJMCH, Schäfer W. Scoring the ICSmaleSF questionnaire. Journal of Urology. 2000; 164: 1948-1955.
[29] 1994 Cancer Statistics, registrations (Series MB1 no. 27). London: The Stationery Office, 2000.
[30] Moss S, Draper GJ, Hardcastle JD, Chamberlain J. Calculation of sample size in trials of screening. International Journal of Epidemiology 1987;16:104-110.
[31] Ukoumunne OC, Gulliford MC, Chinn S, Sterne JA, Burney PG. Methods for evaluating area-wide and organisation-based interventions: a systematic review. Southampton: 1999.
[32] Hayes RJ, Bennett S. Simple sample size calculation for cluster-randomized trials. International Journal of Epidemiology 1999;28:319-326.
[33] de Koning HJ, Auvinen A, Berenguer Sanchez A, et al. Int J Cancer 2002; 98: 268-273
[34] Melia and Moss. B J Cancer 2001; 85(5): 656-657.
[35] de Koning HJ, Auvinen A et al for the ERSPC and PLCO trials. Large-scale randomised prostate cancer trials: Program performances. Int. J. Cancer 2002; 97: 237-44.
[36] Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472-1477.

CAP study

Cluster randomised triAl of prostate specific antigen (PSA) testing for Prostate cancer

Protocol Version 9

Post 10 year follow-up

2020

Principal Investigators:

RM Martin[1] (Lead Principle Investigator)

JL Donovan[1]

FC Hamdy[2]

DE Neal[2]

Trial Co-ordinators:

EL Turner[1]

CR Metcalfe (Deputy)[1]

[1] Population Health Sciences, Bristol Medical School, University of Bristol, Bristol BS8 2PS
[2] University of Oxford, Nuffield Department of Surgical Sciences, Oxford, OX3 9DU

Study Coordinator

Dr Emma Turner, Population Health Sciences, Bristol Medical School, University of Bristol, Canynge Hall, 39, Whatley Road Bristol BS8 2PS Tel: 0117 928 7270, Fax: 0117 9287325, email: emma.turner@bristol.ac.uk

Deputy Study Coordinator

Dr Chris Metcalfe Population Health Sciences, Bristol Medical School, University of Bristol, Canynge Hall, 39, Whatley Road Bristol BS8 2PS Tel: 0117 9287326, Fax: 0117 9287325, email: Chris.Metcalfe@bristol.ac.uk

Principal Statistician

Dr Jonathan Sterne, Population Health Sciences, Bristol Medical School, University of Bristol, Canynge Hall, 39, Whatley Road Bristol BS8 2PS Tel: 0117 9287396 email: jonathan.sterne@bristol.ac.uk

Primary Care Recruitment

Dr Kerry Avery, Population Health Sciences, Bristol Medical School, University of Bristol, Canynge Hall, 39, Whatley Road Bristol BS8 2PS Tel: 0117 9287233 email: kerry.avery@bristol.ac.uk

Trial Registration: ISRCTN92187251

Contents

Figures

Figure 1: Trial design

Abbreviations

CAG = Confidentiality Advisory Group
CC = Clinical Centre
CODE = Cause of Death Evaluation
CNR = Case Note Review
DOH = Department of Health
DSPT = Data Security and Protection Toolkit
EHR = Electronic Health Record(s)
ERSPC = European Randomised Study of Screening for Prostate Cancer
HES = Hospital Episode Statistics
HTA = Health Technology Assessment
NCRAS = National Cancer Registration and Analysis Service
NHSD = NHS Digital
PCT = Primary Care Trust
PEDW = Patient Episode Database for Wales
PHS = Population Health Sciences, Bristol Medical School
PIAG = Patient Information Advisory Group
PLCO = Prostate, Lung, Colorectal and Ovarian cancer screening trial
ProtecT = Prostate Testing for Cancer and Treatment
SAIL = Secure Anonymised Information Linkage databank
SLSP = System Level Security Policy
SOP = Standard Operating Procedure

1. Scope

This protocol provides an outline of the trial background, rationale and methodology for the follow-up period post 10 years, whilst continuing to include processes that are now complete and are not active as part of the post 10 years follow up period for reference purposes.

Technical and operational elements are subject to regular re-specification, therefore separate Standard Operating Procedures (SOPs) are summarized and referenced here only. All SOPs are available on request. The appropriate ethical regulatory bodies will be notified of any major changes that require a change in trial protocol.

2. Introduction

Background to study

Few international issues in health care are as controversial as prostate cancer screening. Prostate cancer has a major impact on public health in the UK. There were over 11,800 deaths from prostate cancer between 2016-2018, making it the second leading cause of cancer mortality in men (1). The aetiology of prostate cancer remains unclear and opportunities for primary prevention are limited. Developments in diagnostic tests for prostate cancer, in particular the introduction of PSA testing, have led to increased interest in the possibility of secondary prevention through population screening. Screening to identify prostate cancer while it is localised to the gland has provoked much public and scientific attention and there is intense debate about its role in improving men's health. Current UK health policy does not advocate population screening, but the policy remains under active review by the National Screening Committee. Major concerns remain about the lack of evidence about the effectiveness of treatments (the rationale for the ProtecT treatment trial) and the potential for diagnosis and over-treatment of tumours that might never become clinically significant. The ProtecT trial demonstrated that there was no difference in prostate cancer mortality between those treated for localised prostate cancer with prostatectomy, radiotherapy and active monitoring (2).

International publications have further fuelled the debate about population screening. The Scandinavian treatment trial showed a 50% reduction in prostate cancer mortality following radical prostatectomy compared with watchful waiting for ‘early prostate cancer’, but there was no significant difference in all-cause mortality, and fewer than 5% presented following screening with the PSA test, thus limiting its relevance to screen-detected men (3). An observational study of two fixed cohorts in the US showed significant increases in diagnosis and treatment of prostate cancer in intensively screened Seattle compared with non-screened Connecticut, but there was no difference in prostate cancer mortality over 11 years of follow-up (4).

Despite evidence from a large European trial (ERSPC, n = 162,243) (5), the value of PSA-based screening is hotly debated, resulting in different policies worldwide (6, 7). The controversial US Preventive Services Task Force review (6, 8), considering the totality of evidence including results from a US trial (PLCO, n=76,693) (9), found limited prostate cancer mortality benefit; insufficient to outweigh the risks of overtreatment and harms. New evidence from ProtecT shows that adverse screening impacts include biopsy side-effects (10), and distinct treatment effects on urinary, sexual and bowel function (11), for no treatment-related mortality benefit after 10-years (2). Concerns exist, however, about the quality of existing evidence (12), set alongside recent treatment-related reductions in metastases (2), favourable modelling projections of alternative screening strategies (13, 14), new secondary analyses (15, 16), greater absolute benefits with long-term follow-up in ERSPC (5), increasing use of active monitoring to delay radical treatment (11), and between-country heterogeneity (17). Such complexities confuse men

(18) and are difficult to communicate (19, 20). These issues indicate that the 'benefit-to-harm trade-off' is unresolved with current evidence.

Findings after 10 years

After a median follow-up period of 10 years, the CAP trial demonstrated that there was no significant difference in prostate cancer mortality between men who were invited to a single PSA screening blood test (intervention group) and those following standard NHS care (control group), although detection of low-risk prostate cancer cases increased in the intervention group (21). As a result, the introduction of routine population-level prostate cancer screening in the UK is not recommended and remains under regular review by the UK National Cancer Screening Committee.

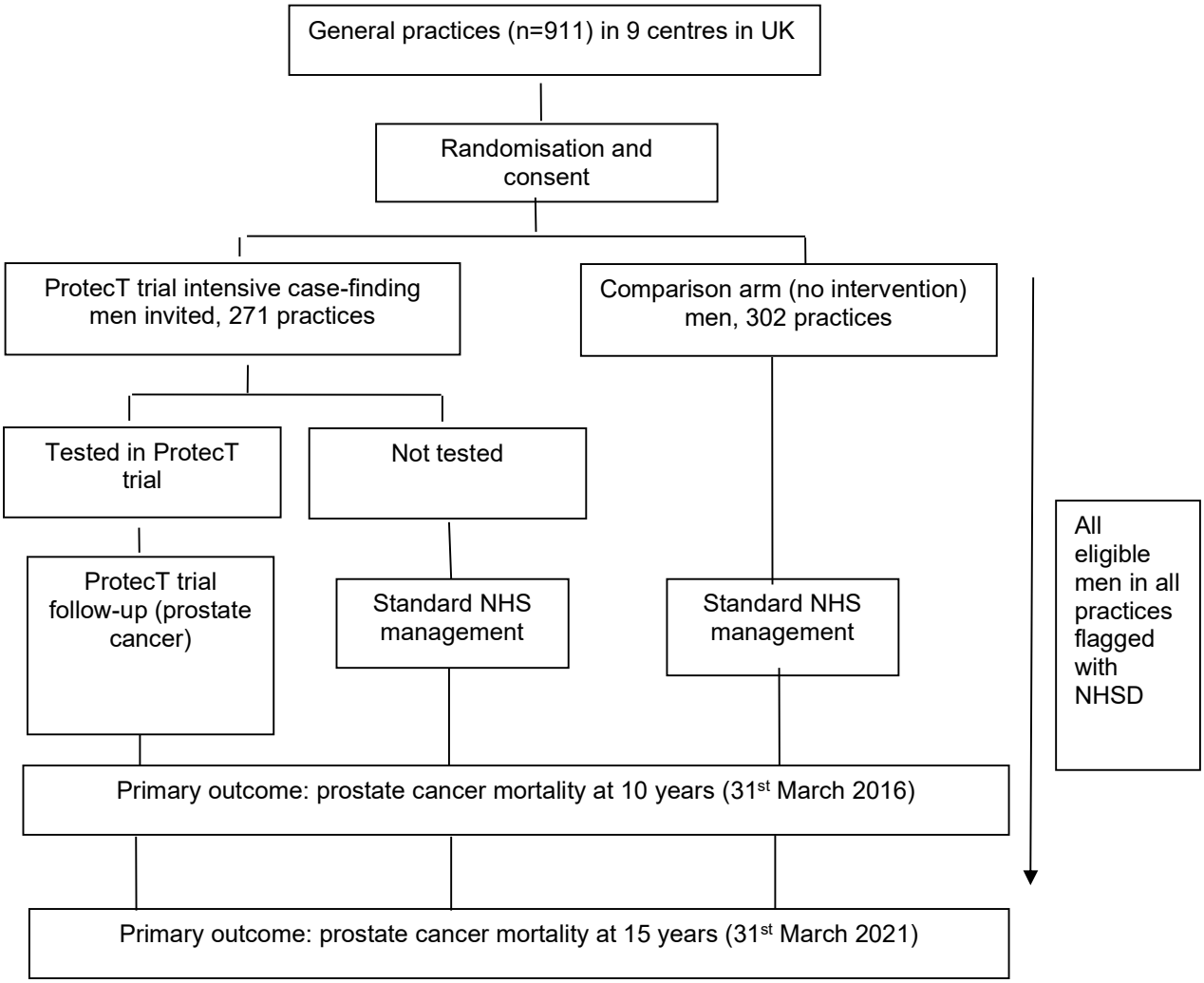
The need for continued follow-up

The complexity of the issues involved in prostate cancer screening make it timely to extend CAP to allow the assessment of the potential impact of population screening for prostate cancer in the UK. The differences in aspects of design between the CAP extension and the ERSPC and PLCO studies in terms of the methods of recruitment, screening tests and treatments offered (see Table 1) will allow wider exploration of the issues and also provide opportunities to both pool and compare findings. The design of the CAP extension will lead to lower levels of contamination and more precise estimates of screening effectiveness. Further, where controversy is as great as it is in relation to prostate cancer screening, and the potential investment so large, there are considerable strategic advantages in conducting this UK trial. It will add to international understanding of the cost-effectiveness of the secondary prevention of prostate cancer, but, more parochially, assist with policy development in the UK.

Table 1 Major design aspects of the two ongoing screening trials (22) and CAP

	ERSPC	PLCO	CAP
Age range	55-69 years (core group) Some 50-54, 70-74 years	55-74 years	50-69 years
Design	Individual randomisation	Individual randomisation	Cluster randomisation
Participants	Most randomly selected from population registries. Some volunteers	Volunteers	All individuals from randomly selected general practices
PSA threshold	3.0ng/ml or 4.0ng/ml (varies by centre)	4.0ng/ml	3.0ng/ml
Screening interval	4-yearly (some 1, 2 years)	1 year	Single screen
Percent PSA raised	7-15% (varies by centre)	16%	11%
Cancers detected per 1,000 screened	11-42 (varies by centre)	Not available	12
Treatment regimen in screened group	Variable usual care (radical advised)	Variable usual care (radical advised)	Randomised (surgery, radiotherapy, active monitoring)

Trial design – post 10 years follow-up (Figure 1)



3. Aims

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.

4. Objectives

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.

5. Study design

This cluster-randomised trial consists of two arms:

a) The intervention arm - The NHS HTA funded ProtecT treatment trial. This investigates the effectiveness and cost-effectiveness of radical surgery, radical radiotherapy and active monitoring for clinically localised prostate cancer. 233,000 men aged 50-69 years in approximately 400 GP surgeries in nine UK centres (Sheffield, Newcastle, Bristol, Birmingham, Cardiff, Edinburgh, Leeds, Cambridge and Leicester) are being invited to be tested between 2001 and 2008 for the presence of prostate cancer through population based PSA testing.

b) The comparison arm, in which a comparable population of men in approximately 400 GP surgeries in the same UK Centres are not subject to population based PSA testing for prostate cancer.

The CAP cluster randomised control trial consists of two major components:

1) The identification and flagging with electronic health records (EHRs) held and administered by health service data owners (e.g. NHS Digital; NHSD) of i) men taking part in the ProtecT trial ii) men in the intervention arm who neither opted out nor took part in the ProtecT trial, iii) all men in the comparison arm.
2) The review of hospital case notes for men identified as having a probable or possible prostate cancer-related event.

6. Ethical aspects

Ethics

The study will be conducted according to the Declaration of Helsinki 1964, as revised in Tokyo 1975, in Venice 1983 and by the 41st World Medical Assembly, Hong Kong, September 1989.

Ethics Committee Approval

Approval has been given by Derby MREC previously Trent MREC for flagging on 12th February 2004, and for obtaining consent to review hospital case notes on 24th November 2005. This approval is given under section C of the DoH 'No local researcher' guidelines. LREC approval is therefore not needed.
The Confidentiality Advisory Group (CAG) previously the Patient Information Advisory Group (PIAG) granted the study exemption from seeking of individual consent for flagging under section 60: support for use of patient identifiable information of the Social Care Act 2001 on 07/04/2004. CAG under section 60 also granted the study permission to access deceased patients' medical records where consent has not been sought (where the man has died before there was a chance to approach him), or consent was sought but no response was given, on 20/03/2006. This was extended to anonymous linkage with English and Welsh electronic secondary health care records in February 2013 and July 2016, respectively. In July 2016, CAG also granted study exemption from seeking individual consent to access electronic diagnostic stage and grade information for all prostate cancer diagnoses in the trial cohort. Both these exemptions only apply in England and Wales.
The Privacy Advisory Committee for Scotland approved the provision of anonymised lists of individual men linked to their age and general practice for all randomised practices in the trial and the linkage of anonymised, individual data to cancer registrations and mortality files at the Information & Statistics Division Scotland (04/10/2005).

Participant Consent:

6.1.1.Part 1: Flagging

Practices randomised to the intervention arm (ProtecT trial) will be approached and informed consent will be sought from the senior partner for inclusion of the practice. Voluntary individual informed consent for the intervention and for flagging is sought from all men attending prostate check clinics.

Practices randomised to the comparison arm will be approached and informed consent will be sought from the senior partner for inclusion of the practice. Practices that consent will be provided with current information from the NHS prostate cancer risk management programme to advise them of current standard management of prostate cancer.

All GP practices will be asked to put up a poster that will give men the opportunity to opt out of having their records flagged. This poster has been approved by the NHSD and CAG to include all relevant and pertinent information that patients may need to make an informed decision. At the request of NHSD and CAG an updated poster will be displayed in GP practices that were recruited, informing patients registered that the study is happening, providing brief information about the study and informing individuals how to opt-out of the process.

The seeking of individual consent for flagging the details of men in the comparison practices or of men in the ProtecT practices who neither opt out nor participate in the ProtecT trial would threaten the viability of the study. CAG, previously PIAG, have granted the study exemption under section 60 of the Health and Social Care Act 2001 in order to provide the legal basis to do this.

6.1.2.Stage and Grade Collection

Stage and grade are obtained for all men within the trial who have a diagnosis of prostate cancer. CAG section 251 permission allows stage and grade to be transferred from the cancer registry (now National Cancer Registration and Analysis Service NCRAS) without explicit consent. This permission has been extended (20th July 2016) to allow researchers to seek only cancer stage and grade information from medical records (it does not affect our seeking individual consent to extract any further information from the medical records – see section 6.3.3 Case Note Review). Failure to obtain stage and grade data has the potential to introduce important biases in reporting the results of this trial. These biases could reduce the interpretability of the trial results and threaten the trial's impact on informed decision making and public benefit.

6.1.3.Part 2: Case Note Review

Individual informed consent for case note review was previously sought from men who are identified as having had a prostate cancer notification up until September 2016 (see section 12.1).

In 2012, CAG, previously PIAG, have granted the study support under section 60 of the Health and Social Care Act 2001 to review the medical records of men who have died of a cause potentially related to prostate cancer before we could gain their consent (provided the man did not record an objection to their medical records being used for research whilst alive). The following procedure will be followed in order to comply with the conditions of our section 251 support:

a. Research Associates will look for a record of objection during completion of the case note review. If they find one they will cease the completion of the review and destroy the data they have collected confidentially.

7. Study population

General practice enrolment

All GP practices within the catchments of the nine ProtecT clinical centres will be eligible for recruitment, and all men aged 50 to 69 years registered with GP practices in the ProtecT study catchments will be eligible for inclusion.

Randomisation

The details of general practices in Primary care trusts (PCTs) in each of the study areas in England are obtained from the respective organisation (local health care co-operatives in Scotland and local health groups in Wales). General practices within these areas are identified on ordinance survey maps and then assigned to contiguous groups of 10-12 practices. A computer program using the statistical package Stata® is used to allocate an equal (or near-equal) number of practices to intervention (ProtecT) and control groups: this stratified randomisation scheme ensures that the number of intervention and control practices is balanced within geographic areas and primary care groups. A statistician not otherwise involved in the study performs the randomisation process.

8. Inclusion and exclusion criteria

Inclusion criteria

1) All GP practices in the study areas.
2) All men age 50-69 years on the date of preparation of the list at the general practice

Exclusion Criteria

1) 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.
2) GP practices which do not agree to participate, having been randomised, are excluded from the study and analysis. (aggregate follow up for mortality and prostate cancer rates – see section 9.4 below)
3) Control arm practices within clusters where no intervention arm practices were recruited, and intervention arm practices in clusters where no control arm practices were recruited, are excluded.

9. Recruitment of participants

The following describe processes that are now complete and are not active as part of the post 10 years follow up period

Recruitment of general practices (CC and PHS)

All Practices will be contacted by the primary care co-ordinator Kerry Avery or CAP study researchers. The GPs and practice manager will be briefed about the CAP and ProtecT study and an information pack, tailored to the arm of trial to which they have been randomised, will be sent out to each practice. In these information packs the practice will be asked to consent to take part in ProtecT or the comparison arm. For those practices consenting to the ProtecT arm, the ProtecT protocol will follow. For those consenting to the comparison arm, information on prostate cancer risk management programme will follow.

Recruitment of participants (Protect arm)

The ProtecT protocol gives details of inviting participants to attend the prostate check clinic and subsequent process through the trial. In summary, this involves an initial written invitation, followed by a 30-minute prostate check clinic appointment. At this clinic men receive counselling and detailed information about the implications of PSA testing and subsequent treatment. If they consent, blood is taken for a PSA test which is performed only following the receipt of a further 'cooling-off' consent at least 24-hours later. Men with a raised PSA result (≥3.0ng/ml) are invited to attend the urology department for a further PSA, clinical examination, digital rectal examination (DRE) and trans-rectal ultrasound (TRUS)-guided biopsy. Men found to have advanced disease are treated routinely but followed up within the comprehensive cohort. Re-biopsy is offered immediately to those with high grade prostatic intra-epithelial neoplasia (HGPIN) or negative biopsy and a free/total PSA ratio of <0.12. Men with free/total ratio >0.12 or second negative biopsy are offered repeat PSA testing in 12 months. All men with localised prostate cancer (T1-T2, NX, M0) are invited to participate in the treatment trial comparing active

monitoring, radical radiotherapy and radical prostatectomy. If randomisation is not acceptable, a patient-led preference for a treatment option is reached. All men who consent to the ProtecT trial are flagged.

9.1.1. Prospective recruitment of the non responders in the ProtecT practices

The addition of a comparison arm to the ProtecT study means that all other men in the ProtecT practices who have not opted out of the ProtecT study need to be flagged with the NHSCR/HSCIC and local cancer registries.

The Research Assistant will go to the participating GP surgeries and download the name, postcode, date of birth, NHS number and GP practice identification number of all men aged 50-69 years onto the study laptop computer. This list will be saved onto a floppy disk and kept at the practice (this method is detailed in the ProtecT Practices SOP).

The invitation letters will be mailed out as in the ProtecT protocol.

Once the Prostate check clinics (PCC) have finished in the practice, the PCC schedules are returned to Smed for data entry and storage. At this point, all the consent pages of the PCC schedules need to be entered prospectively, in order to identify those men who opt out.

Definition of opt out and NOT flagged.

1) Those men who explicitly refuse thePCC invite, once they have received information about the study.

2) Those men who explicitly refuse at the PCC to have a PSA test as part ofthe ProtecT study

3) Those men who do not refuse to participating in the ProtecT study, but say No to having their records flagged.

4) Men in the ProtecT practice who have requested to be excluded on seeing the poster displayed in the General Practice.

A list of the name, postcode, date of birth and NHS number will be created for each practice of all men participating in and opting out of the ProtecT study. The Research Assistant will return to the participating GP surgeries and reconcile the two lists (this method is detailed in the ProtecT Practices SOP). The details of men to be flagged will be transferred to SMed to enable flagging to be initiated.

9.1.2. Retrospective recruitment of non-responders in the ProtecT practices

Retrospective flagging: Practices who have been involved with the ProtecT study will be returned to and the poster will be displayed in the practice for three months.

If in these practices the original list of men is available, then the Research Assistant will need to reconcile the original list with the list of men who participated or opted out of the Protect trial.

If the original list of men is not available then the Research Assistant will reconstitute the list of men as near to possible to the time of the creation of the original list. The two lists will then be reconciled.

Recruitment of participants (Comparison arm)

Using the method detailed in the CAP Practices SOP, the research assistant will approach practices randomised to CAP in order to obtain consent. The research assistant in each centre will visit the consented practice to liaise with practice staff, and put up the poster. The practice will be given the CaP download protocol. In order to ensure in each cluster the same calendar period is covered in the ProtecT and CAP practices, the CaP practices will either be asked to produce a list of men in the age range 50-69 years who were at the surgery at a particular point in time or a current list of men. (see Appendix 2 for details).

The research assistant will return to the practice after three months and will exclude any man who has requested not to be flagged on seeing the poster displayed in the General Practice. The name, postcode, date of birth, NHS number and GP practice identification number of all men on this list will be transferred to SMed to enable flagging to be initiated.

All general practices participating in CAP or ProtecT will be sent a letter thanking them for their involvement and informing them that we will be returning to the practice to seek consent from men for the case note review part of the study (CAP acknowledgement letter v2_20070727 or ProtecT acknowledgement letter v1_15.08.06).

Aggregate data on groups not in routine follow up.

In cases where individuals are not in routine follow up:

1) Those described above 9.2.1 who explicitly refused to take part upon receipt of their reply slip or who declined to participate when attending PCC. In these cases there is a possibility that these individuals may have a greater likelihood of being diagnosed with prostate cancer or dying within 10 years follow-up.

2) Also GP practices which do not agree to participate, having been randomised, are excluded from the study and analysis (section 8 exclusion 3). We have been advised by the DMC that in interpreting the study results it will be beneficial if we were able to comment on the overall rate of death and cancer diagnoses in men aged 50-69 years in those practices.

CAG have given permission (letter dated 20th July 2016) for us to obtain aggregate data from HSCIC for mortality and prostate cancer diagnoses in 5 year age bands. We do not need individual level data. These tables of aggregate data will be returned to School of Social and Community Medicine (SSCM) at the University of Bristol.

10. Flagging of men's details with local cancer registries and NHS Digital

The lists obtained from the GP practices will be imported into the admin database. At this point any manipulation needed to standardise the data will be performed. Any duplicates will be identified at this point and dealt with. The information will then be imported into the main template. At this point a unique identifier will be allocated to each of the men to signify the arm of the study they are in, the research centre and the GP practice.

The name, postcode, date of birth, NHS number and unique identifier will then be transferred to the NHS Information Centre (NHSIC)/Health and Social Care Information Centre (HSCIC) / Public Health England NCRAS, and local cancer registries, where they will be flagged.

Identification of a prostate cancer related event

Surveillance for relevant outcomes will be passive and triggered by the occurrence of deaths or cancer registrations in the flagged group.

Once information about a prostate cancer related event has been received, the following information if available will be entered into the template: Date of prostate cancer registration; Hospital where diagnosis occurred; Man's consultant; Cause of death (text); Original underlying ICD code; Multiple original ICD code and Stage and grade of tumour.

This information will be anonymised using the unique identifier.

11.SAIL Hospital Episode Statistics (HES) and Patient Episode Database for Wales (PEDW) Data

To carry out a budget impact analysis from the perspective of NHS England secondary care. Hospital Episode Statistics (HES) data (anonymised via the SAIL Gateway [http://www.adls.ac.uk/secure-anonymised-information-linkage-databank/], located at the Health Information Research Unit (HIRU), Swansea University) will be used to compare the inpatient and outpatient costs (*i.e.* the key secondary care cost drivers) in the 'screened' and 'unscreened' arms in England.
CAG noted (letter dated 27th February 2013) that "following this method (details appendix 7) would result in no further disclosure of patient information, as SAIL would hold a pseudonymised dataset and provide researchers with only the data that they required for analysis purposes. Researchers would have no access to the study ID and therefore could not link data held already about trial participants." Therefore they concluded that no amendment was required to the existing s251 approval.

HSCIC approved this methodology (letter from the NIGB dated September 2016) and agreed to supply Hospital Episode Statistics Admitted Patient Care; Hospital Episode Statistics Critical Care; Hospital Episode Statistics Accident and Emergency; Hospital Episode Statistics Outpatients; Hospital Episode Statistics Diagnostic Imaging Dataset for the complete cohort being flagged and followed up in the trial

For individuals from the Welsh clinical centre linkage to the Patient Episode Database for Wales (PEDW) has been granted by CAG and SAIL as these individuals would not have Hospital Episode Statistics (HES) data (Appendix 7).

12.The Case Note Review

Men who are identified by flagging as having had a prostate cancer diagnosis we will collect data from case notes for three major purposes:

1) to ensure we determine as accurately as possible the cause of death in men diagnosed with prostate cancer
2) to ensure accurate determination the progression and outcome of prostate cancer
3) to ensure accurate determination of the diagnostic and treatment pathways

Participant consent procedure

The following describe processes that are now complete and are not active as part of the post 10 years follow up period

Initially, the man's GP will be contacted and asked to indicate whether the man is alive and currently fit enough to be approached (see **GP letter&consent formV1.1_09.04.09**. A slightly different letter is sent when a man has moved from a participating practice to a non-participating practice - **GP(other)letter&consent formV1.1_09.04.09**).

1) men whom the GP indicates are well enough (i.e. not terminally ill or currently temporarily unwell) will be contacted by post by the GP, who will send an invitation letter to the man (on practice headed notepaper, signed by the GP), an information sheet and two copies of a consent form (see **Patient Invitation letter(GP)V2.1_07.04.09**, **Patient Information sheet(GP)V5_20160728** & **Patient Consent form(GP)V3_20070723**).

The men will be asked to carefully read the information sheet and complete the consent form. The consent form has been designed to give the man the following options:

a) to agree to take part in the study

b) to seek further information about this study, either from a study researcher, or at a face-to-face appointment with the man's GP or the practice nurse. If the man seeks a face-to-face appointment with the GP or practice nurse, face-to-face consent will be obtained from the man at the time of this appointment. A covering letter (see **Appointment cover letter to GP or nurse v1 09.03.06)** and appointment feedback form (see **Appointment feedback form v1 09.03.06),** along with the **Patient Invitation**

letter(GP)V2.1_07.04.09, **Patient Information sheet(GP)V5_20160728** & **Patient Consent form(GP)V3_20070723**), will be sent to the GP or practice nurse prior to this appointment.

c) to indicate that he does not wish to participate in the study to access his medical records, in which case he will be excluded from the study.

The man will be asked to keep a copy of the consent form and the information sheet for his records.

On occasions if a GP has expressed a wish that s/he does not want to offer the man a face-to-face appointment, adapted versions of the documentation, which remove this option, will be used. (see **Patient Invitation letter (GP no contact)V1.1_09.04.09, Patient Information sheet (GP no contact)V2_20160728,Patient Consent form (GP no contact)V2_20070723)**

If it is not possible to contact the man via the GP, the treating urologist or oncologist will be asked to request consent (see **Cons letter&consent (ProtecT)V2.1_09.04.9**, **Cons letter&consent (non-ProtecT)V2.1_09.04.09, Patient Invitation letter(cons)V2.2_20101102.doc, Patient Information Sheet(cons)V5_20160728, Patient Consent form(cons)V3_20070723)**. Slightly different wording is used depending on whether the consultant is based at a hospital participating in the ProtecT trial or not).

There are second versions of each letter to GPs, consultants, and participants which are sent as reminder letters if we do not receive a response after 3 weeks.

2) if the man has died before we can gain consent for note review

a) We will check whether or not the man had been contacted while alive and had not responded to a request for consent

bi) For non-responders to a request for consent, a letter will be sent to the GP of the deceased man asking whether a record exists of the man having objected to his medical records being reviewed for the purposes of medical research (see **GP letter&consent form_dec_v1.1_20090408).** A slightly different letter is sent when a man has moved from a participating practice to a non-participating practice - **GP(other)letter&consent form_dec_v1.1_20090408**).

bii) For non-responders to a request for consent in cases where the GP declines to participate, or states that records have been returned to the PCT, a letter will be sent to the PCT asking whether a record exists of the man having objected to his medical records being reviewed for the purposes of medical research (**see PCT letter&consent form_dec_v1_20120529**).

c) For responders who had declined to consent, we will **not** proceed.

d) For all other men (i.e. i) those not contacted while alive; and ii) responders who had consented while alive) we will proceed with note review. If an indication of dissent for use of data for research is found in any medical record then these should not be used, regardless of which group the patient falls into.

Data collection once a prostate cancer-related event or death has been identified

The following describe processes that are now complete and are not active as part of the post 10 years follow up period

See CNR Data Extraction Proforma, Guidelines and Data Dictionary for complete record of current data collection.

The data to be collected are details and dates of: symptoms and signs of prostate cancer presence and progression, diagnostic and monitoring tests, histological grade of cancer, tumour stage, treatments received and outcome, complications of prostate cancer and its treatment, co-morbidities, and other resource use data related to prostate cancer diagnosis and treatment not otherwise covered by the above variables (length of inpatient stay, outpatient appointments). This data will be abstracted onto a standardised proforma by trained research assistants. It will be supplemented by scanned copies of relevant inpatient and outpatient medical records, including in-patient notes in

the last 2 months before death, pathology / radiology reports, and copies of discharge and outpatient letters detailing important co-morbidities and evidence of prostate cancer progression / metastases.

These data and scanned documents will be fully anonymised.

Cause of Death Review

For men in the study who have died of a cause potentially related to prostate cancer, summary vignettes will be submitted to the Cause of Death Evaluation (CODE) Committee. The aim is that data supplied for the death review should be identical, whether the individual had a screen-detected cancer or not. Thus any mention of the ProtecT trial, cancer screening tests, and initial clinical presentation (both screen-detected and symptomatic) will be removed to ensure reviewers are blind as to the allocation in the trial.

In order to ensure comparability of information with the ProtecT trial and to allow accurate ascertainment of cause of death, the same endpoint committee as for the ProtecT trial will be established **(Chair** Professor Peter Albertsen**).** They will be blinded to the arm of the trial and will scrutinise death certificates to assign an underlying cause of death. Independent members have been invited to join including representatives from the Scandinavian trials (Professor Jan Adolfsson) and PLCO (Peter Albertson, USA), all of whom have already developed relevant proformas and algorithms for ascertainment.
See PROTOCOL for determining cause of death and Data Dictionary.

13.Outcome measures

Primary outcome

Prostate cancer mortality at 15 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. 'Fifteen years' is the point in time when the median follow up period for men in the study is fifteen years, which is anticipated to be the end of March 2021. Allowing a six 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 31st March 2021, and which we have received notification of by 30th September 2021. Only outcome events for which we receive notification from the UK National Statistics Office will be included in the main analyses.

Secondary Outcomes

The outcomes will be evaluated in the following way

13.1.1. All cause mortality

Notification of death will be received from NHS Digital who manage and distribute death registration data. For more details see Processing data from NHS Digital SOP.

13.1.2. Prostate cancer mortality

Given the problem of ascertainment bias in attributing cause of death (23), as a consequence of both prostate cancer detection and possibly treatment (24), a cause of death committee will be established (see section 12.3 and See PROTOCOL for determining cause of death).

13.1.3. Disease status

Stage and grade of prostate cancer will be received from cancer registry data separately for England and Wales and therefore dependent on securing good quality data from routine sources.

13.1.4. Prostate cancer metastases

This outcome is dependent on securing good quality data from routine sources

13.1.5. Effectiveness and cost-effectiveness of alternative screening programmes

The empirical trial results will be used to refine the structure of, and update the evidence-base for, a Markov-based decision-analytic model of disease progression to simulate the lifetime effectiveness and cost-effectiveness of prostate cancer screening.

13.1.6. Lead time and over-diagnosis

Over-diagnosis will be directly observed as the excess prostate cancer incidence in the screened relative to control arm, once lead time has ensued, accounting for age-specific diagnosis rates and year-on-year increases in prostate cancer incidence apparent from the comparison arm.
Prostate cancer screening lead time has been indirectly estimated at 12 years, an empirical, trial-based estimate of lead time requires further follow-up. The extension to 15-years median follow-up will result in all men having a minimum 12-year follow-up, allowing precise estimates of age-specific lead time.
Over-diagnosis will be directly observed as the excess prostate cancer incidence in the screened relative to control arm, once lead time has ensued, accounting for age-specific diagnosis rates and year-on-year increases in prostate cancer incidence apparent from the comparison arm. The plausibility of over-diagnosis estimates will be assessed for consistency with lead time estimates.

14.Analysis

For more details see 15-year Statistics Analysis Plan (25).

The primary analysis will be based on those deaths classified as from prostate cancer by the independent panel. Random-effects Poisson regression models (also known as negative-binomial regression models) will be used to estimate rate ratios comparing prostate cancer mortality in intervention and comparison practices, allowing for clustering by including the general practice of each participant as a random effect. These methods will also be used to estimate rate ratios comparing all cause mortality and prostate cancer mortality in intervention and control practices, and also comparing “probable” or “possible” prostate cancer deaths, should the independent panel decide to classify some deaths in this way. The relatively large number of practices randomised, and the stratified randomisation scheme, should ensure that practices are approximately balanced with respect to prognostic factors such as socio-economic position (using Jarman or Townsend scores) at the time of randomisation. However, we will conduct sensitivity analyses to confirm that controlling for any imbalances makes little or no difference to the estimated rate ratios comparing intervention and control practices.

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 used the optimal treatment(s). 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 extended study.

Other analysis of interest could include a comparison of underlying rates of prostate cancer in men who do and do not consent to screening. This would be derived by comparing rates in men in intervention practices who do not attend for case-finding with those in control practices, assuming that men in the control practices represent comparable populations of men who would and would not have consented to screening if invited.

15.Economic Evaluation

The economic evaluation will be led by Dr Sian Noble (PHS)

We plan to conduct a trial-based analysis to assess the affordability of introducing a PSA screening programme for prostate cancer in the UK. A budget impact analysis will be prepared from the perspective of NHS England secondary care. Hospital Episode Statistics (HES) data (anonymised via the SAIL Gateway) will be used to compare the inpatient and outpatient costs (*i.e.* the key secondary care cost drivers) in the 'screened' and 'unscreened' arms in England. Costs will be extrapolated to estimate the cost to NHS England at a population level, with adjustment to allow for potentially differential uptake of the screening invitation in practice. Costs will be assessed over five years post-randomisation, and results will be presented per year.

The empirical trial results will be used to refine the structure of, and update the evidence-base for, a Markov-based decision-analytic model of disease progression to simulate the lifetime effectiveness and cost-effectiveness of prostate cancer screening. The existing model is limited by: the quality and availability of UK specific data for several parameter inputs, currently only informed by a mix of expert opinion, literature and assumptions; the absence of quality-adjusted life years (QALYs), important as prostate cancer treatment causes sustained reductions in quality of life; and the omission of Gleason grade, a key prognostic indicator.

16.Health Related Quality of Life

The following describe processes that are now complete and are not active as part of the post 10 years follow up period

The HRQL will be co-ordinated by Miss Jane Blazeby, see Appendix 1 for details

17. Contamination

The following describe processes that are now complete and are not active as part of the post 10 years follow up period

A sub-study has established the rate of PSA testing in a sub-sample of CAP practices in 2009 (previously described in the CAP Protocol v8 20/12/2016). Our study estimated the annual practice-based PSA testing rate for men aged 45–89 years with no previous diagnosis of prostate cancer at 6.2% during 2007 (26).

The PSA testing rate in the UK over a 10 year period has also been investigated by the CAP team. This analysis demonstrated that a high proportion of men aged between 45-69 years old did undergo PSA testing, but that this was to investigate lower urinary tract symptoms, rather than as prostate cancer screening (27).

18.Data management and security

Data held in PHS will conform to the University Information Security Policy (http://www.bris.ac.uk/infosec/policies/), and according to Department of Health research governance standards.

The CAP study data management and security systems comply with the NHS Data Security and Protection Toolkit annual assessment. For more information, please refer to the CAP System Level Security Policy (SLSP) and the CAP Data Protection and Security Toolkit (DSPT) documentation (ref EE133799-SSCM-CPCSCAPS).

19.Management, ethical considerations and study organisation

Trial Steering Committee (ProtecT and CAP)

The following describe processes that are now complete and are not active as part of the post 10 years follow up period

A Trial Steering Committee oversaw the CAP trial until March 2017 when the Committees were dissolved. Written records will be taken of each meeting and copies held by the study coordinator.

- Chair: Professor M Baum (London)
- Prof A Zeitman (external radiographer, USA)
- Dr D Dearnaley (clinical oncologist/radiotherapist, London)
- Dr J Adolfsson (external urologist, Sweden)
- Prof P Albertsen (external urologist, USA)
- Dr M Robinson (uro-pathologist, Newcastle-upon-Tyne)
- Professor M Mason (oncologist, Cardiff)
- ProtecT and CAP Principal investigators (Professors F Hamdy, J Donovan, D Neal, Dr R Martin)
- ProtecT and CAP study senior statisticians (Professor T Peters, Dr J Sterne)
- ProtecT study coordinator (Dr A Lane, Bristol)
- CAP study coordinators (Dr E Turner, Dr C Metcalfe, Bristol)
- Health Economist (Prof T Roberts, Birmingham)
- ProtecT and CAP health economists (Dr S Noble, Bristol & Dr J Wolstenholme, Oxford)
- ProtecT Coordinating Nurses (Mr P Holding, Sheffield; Ms T Lennon, Newcastle; Ms S Bonnington, Leicester)
- Professor F Schroder (CAP external urologist, The Netherlands)
- Professor T Walley (HTA Director)
- Dr Jon Oxley, (Bristol (ProtecT Histopathology Lead)
- Observers from the NCCHTA

The TSC will meet annually in January.

CAP Data Monitoring Committee (DMC)

The Data Monitoring Committee does not actively convene beyond the 10-year analysis phase but can be recalled during the 15-year analysis period, if necessary.

- Chair: Professor Lars Holmberg (Clinical Epidemiology)
- Professor Simon Thompson (Statistician); Professor Usha Menon (Gynecologist and Epidemiologist); Professor Rob Pickard (Urologist)

The following describe processes that are now complete and are not active as part of the post 10 years follow up period: Recommendations from the DMC regarding the stopping rules for the study will be taken to the TSC for ratification. The DMC will meet annually unless otherwise necessary. A report will be sent to the TSC with the recommendations from each DMSC meeting. The TSC can invite the DMSC Chair or his representative to attend the TSC if deemed appropriate.

Study Management Committee meetings

All applicants will meet on a regular basis to oversee the project providing expertise as appropriate. Written records will be maintained of these meetings

19.1.1. Terms of reference

The Management Committee act as an advisory group for the trial. The Committee provides:

- oversight of the scientific and methodological conduct of the 15-year analysis phase of the trial.
- Insight into how to maximise the value and impact of the trial
- Specific advice if requested by the trial team.

Management Executive Committee

- Professors Martin, Donovan, Hamdy, Neal, and Dr Sterne comprise the committee
- All publications using CAP data must be approved by the committee prior to submission of the publication
- The committee retains the decision to publish or communicate study results
- The content of all presentations at scientific meetings using CAP data must be notified to the committee prior to presentation
- The details of publications and presentations at scientific conferences should be notified to the study coordinator a copy of the paper sent on publication

Organisation of study documentation

All clinical centres will have an investigators' Trial Master File, which will include all relevant information and documentation for the trial. This will include the protocol, financial agreements, CVs of all staff involved in the trial, and any correspondence or emails received pertaining to the study. All documentation is now held centrally at PHS. Electronic copies are available on request.

20.Publications

Annual reports will be produced for Cancer Research UK. Papers will be prepared for publication in general, epidemiological and urological peer-reviewed journals. The findings will also be presented at national and international conferences.

The primary analyses have been undertaken at 10-year follow-up (21).

The primary analyses will be repeated at a median of 15-years follow-up as per the 15-year Statistical Analysis Plan (25).

21.Reference List

1. UK CR. Prostate cancer mortality statistics 2021 [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/mortality.
2. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016;375(15):1415-24.
3. Holmberg L, Bill-Axelson A, Helgesen F, Salo JO, Folmerz P, Haggman M, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. N Engl J Med. 2002;347(11):781-9.
4. Lu-Yao G, Albertsen PC, Stanford JL, Stukel TA, Walker-Corkery ES, Barry MJ. Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut. BMJ. 2002;325(7367):740.
5. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Zappa M, Nelen V, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet. 2014;384(9959):2027-35.
6. Chou R, Croswell JM, Dana T, Bougatsos C, Blazina I, Fu R, et al. Screening for prostate cancer: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2011;155(11):762-71.
7. Louie KS. Screening for Prostate Cancer Review 2015 Update. Review against programme appraisal criteria for the UK National Screening Committee (UKNSC). 2015.
8. Eggener SE, Cifu AS, Nabhan C. Prostate Cancer Screening. JAMA. 2015;314(8):825-6.
9. Andriole GL, Crawford ED, Grubb RL, 3rd, Buys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009;360(13):1310-9.
10. Rosario DJ, Lane JA, Metcalfe C, Donovan JL, Doble A, Goodwin L, et al. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. BMJ. 2012;344:d7894.
11. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med. 2016;375(15):1425-37.
12. Carlsson S, Vickers AJ, Roobol M, Eastham J, Scardino P, Lilja H, et al. Prostate cancer screening: facts, statistics, and interpretation in response to the US Preventive Services Task Force Review. J Clin Oncol. 2012;30(21):2581-4.
13. Etzioni R, Gulati R, Cooperberg MR, Penson DM, Weiss NS, Thompson IM. Limitations of basing screening policies on screening trials: The US Preventive Services Task Force and Prostate Cancer Screening. Med Care. 2013;51(4):295-300.
14. Gulati R, Mariotto AB, Chen S, Gore JL, Etzioni R. Long-term projections of the harm-benefit trade-off in prostate cancer screening are more favorable than previous short-term estimates. J Clin Epidemiol. 2011;64(12):1412-7.
15. Roobol MJ, Kerkhof M, Schroder FH, Cuzick J, Sasieni P, Hakama M, et al. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). Eur Urol. 2009;56(4):584-91.
16. Schroder FH, Hugosson J, Carlsson S, Tammela T, Maattanen L, Auvinen A, et al. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). Eur Urol. 2012;62(5):745-52.
17. Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol. 2010;11(8):725-32.
18. Chapple A, Ziebland S, Hewitson P, McPherson A. Why men in the United Kingdom still want the prostate specific antigen test. Qual Health Res. 2008;18(1):56-64.
19. Evans R, Edwards AG, Elwyn G, Watson E, Grol R, Brett J, et al. "It's a maybe test": men's experiences of prostate specific antigen testing in primary care. Br J Gen Pract. 2007;57(537):303-10.

20. Clements A, Watson E, Rai T, Bukach C, Shine B, Austoker J. The PSA testing dilemma: GPs' reports of consultations with asymptomatic men: a qualitative study. BMC Fam Pract. 2007;8:35.
21. Martin RM, Donovan JL, Turner EL, Metcalfe C, Young GJ, Walsh EI, et al. Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality: The CAP Randomized Clinical Trial. JAMA. 2018;319(9):883-95.
22. de Koning HJ, Auvinen A, Berenguer Sanchez A, Calais da Silva F, Ciatto S, Denis L, et al. Large-scale randomized prostate cancer screening trials: program performances in the European Randomized Screening for Prostate Cancer trial and the Prostate, Lung, Colorectal and Ovary cancer trial. Int J Cancer. 2002;97(2):237-44.
23. Albertsen P. When is a death from prostate cancer not a death from prostate cancer? J Natl Cancer Inst. 2000;92(8):590-1.
24. Newschaffer CJ, Otani K, McDonald MK, Penberthy LT. Causes of death in elderly prostate cancer patients and in a comparison nonprostate cancer cohort. J Natl Cancer Inst. 2000;92(8):613-21.
25. Metcalfe C, Sterne JAC, Martin RM. Cluster randomised triAl of PSA testing for Prostate cancer (CAP) Study: 15 year Statistical Analysis Plan: Version 1.0 13th January 2021. . 2021.
26. Williams N, Hughes LJ, Turner EL, Donovan JL, Hamdy FC, Neal DE, et al. Prostate-specific antigen testing rates remain low in UK general practice: a cross-sectional study in six English cities. BJU Int. 2011;108(9):1402-8.
27. Young GJ, Harrison S, Turner EL, Walsh EI, Oliver SE, Ben-Shlomo Y, et al. Prostate-specific antigen (PSA) testing of men in UK general practice: a 10-year longitudinal cohort study. BMJ Open. 2017;7(10):e017729.

Appendix 1

Evaluating population-based screening for localised prostate cancer in the United Kingdom: impact on quality of life and men's experiences in the ProtecT study

Co-ordinator: Miss Jane Blazeby

Purpose

Population screening for prostate **cancer** is controversial and not currently advocated in the UK. Policy decisions about the introduction of such a programme require data about benefits and risks of screening and how these impact on health-related quality of life (HRQL) and health behaviour. The recent funding by Cancer Research UK has converted the ProtecT trial (Prostate testing for cancer and Treatment trial), funded by the NHS Health Technology Assessment Programme into the intervention arm of a primary care based, cluster randomised trial of prostate cancer screening. Practices in nine centres in the UK are randomised to be invited for PSA testing, flagged with the NHS central registry and enter the ProtecT treatment trial, or the comparison arm (standard care, no systematic screening and eligible men are flagged). This additional study will investigate the impact of screening on men's health related quality of life (HRQL), to explore mens' experiences during the screening process and to identify factors that predict uptake of screening.

Background

Screening for prostate cancer

Screening for cancer carries with it risks for increased distress and physical side effects among the screened population related to invitations, experiences of tests, waiting for results and choosing treatment if disease is detected. Screening also carries advantages, because detection and effective treatment of cancer could potentially reduce the incidence of end-stage disease and associated deterioration in physical and psychosocial health and cancer-related mortality. Assessment of risks and benefits requires measurement of morbidity related to tests and treatment, measurement of reduction in prostate cancer mortality and measurement of how screening and treatment impact on HRQL. Understanding how men interpret risks and how these influence health behaviour is valuable because it is evident from the literature that uptake of screening can be influenced by a range of factors; including demographic characteristics, distress, patients' knowledge and health beliefs and cultural expectations of health care[1-3].

International screening studies in prostate cancer

There are two international trials of population screening for prostate cancer, the European Randomised Study of Screening for Prostate Cancer (ERSPC) and the US Prostate, Lung, Colorectal and Ovarian Cancer Trial (PLCO)[4,5]. They differ in design to the UK study, and it is expected that the UK study, ProtecT and CR UK funded recent extension, will provide advantages for UK policy makers because of a lower contamination rate (due to the cluster randomised design), a more robust evaluation of treatment (through the ProtecT randomised treatment trial), and its setting within the UK NHS health care system[6]. A framework for assessment of HRQL in the international trials has been described, but data are only being collected in one centre (Rotterdam) within ERSPC and HRQL results have not yet emerged from the North American study[7,8].

Data from Rotterdam have shown that screening for prostate cancer, probably has minimal short or long term HRQL effects[9]. Transient distress and symptoms related to biopsy do not impact on overall HRQL scores, apart from in men who are predisposed to anxiety. There is also some evidence, that a negative result after prostate biopsy reduces anxiety[9]. Results from the treatment part of ERSPC show that HRQL

scores are better in men with screen detected cancers that in men with clinically diagnosed lesions, related to earlier disease stage and perceived benefits of earlier cancer detection[10]. However, longitudinal data before and after diagnosis of screen detected prostate cancer does appear to show a negative impact on mental health scores (SF36) during the first six months[11]. In the non-randomised treatment part of ERSPC, HRQL scores after surgery and radiotherapy for localised prostate cancer have been reported [12]. They show similar findings to others that different treatment modalities have significant detrimental effects of different functional aspects of health (e.g sexual function)[13]. There are no comparisons of HRQL impact from randomised studies of screen-detected prostate cancer.

The ERSPC trial reports uptake of screening at about 50% (similar to ProtecT). Reasons for non-uptake of PSA testing have been explored in a questionnaire survey (49% response rate)[14]. Results show that men who refuse screening are slightly older, less often married and have a lower level of education than men undergoing PSA testing. These men have less knowledge about prostate cancer and less knowledge about screening with worse general health (but fewer prostatic symptoms). Further understanding of the health behaviour both of men who decline PSA testing and more importantly, men identified with raised PSA results who refuse biopsy (of whom 25% will have cancer) is necessary to inform makers of future health policy. These aspects could easily be investigated as an addition to the ProtecT study.

The added value of HRQL and qualitative assessments during ProtecT study screening

This study will provide considerable added value and advantages to the ongoing international studies and the UK ProtecT treatment trial including:

- HRQL data related to screening that is of greater generalisability to the UK population.
- HRQL data related to screening that links with HRQL from the randomised treatment trial.
- Understanding aspects of men's experiences that influence uptake of screening
- Understanding aspects of men's experiences of screening that will inform HRQL data
- HRQL data which will inform the health economics study to allow estimates of life-time cost-effectiveness in terms of cost per quality adjusted life-year in addition to cost per cancer detected.
- The development of a health beliefs model with validity checking that will provide data to inform future policy makers of barriers to uptake of screening and prostate biopsy.
- HRQL which will allow comparison and synthesis with results from the ERSPC/PLCO groups.

Aim

This study aims to evaluate the impact of screening for prostate cancer on HRQL, to describe men's experiences of screening and to identify predictors of screening uptake. It is not possible to make a single HRQL comparison between screened and unscreened men, because although we have permission to obtain mortality data by flagging with the NHS central registry from unscreened GP pratices (PIAG) we cannot approach individuals because this would contaminate the comparison arm. We therefore propose to study sub-groups of men likely to be most affected by the screening process.

Objectives

1. To evaluate HRQL among subgroups of men who are identified as part of the PSA testing screening protocol in ProtecT, but who currently do not undergo HRQL assessment because they are not relevant to the *treatment* trial outcome.
2. To explore men's experiences of screening using in-depth interviews and understand their interpretation of information and health risk related to prostate cancer screening.

3. To identify predictors of screening uptake (PSA testing) and agreement to prostate biopsy.

Detailed research plan - HRQL and qualitative studies

HRQL is assessed within the ProtecT treatment trial: (1) before the PSA test, (2) at the time of biopsy for those with raised PSA levels to assess the impact of case-finding, (3) six months after randomisation and (4), annually thereafter to evaluate treatment outcome. Qualitative in-depth interviews with men are also performed at these time points within existing funding. This proposal requests support to assess HRQL and perform in-depth interviews in subgroups of men *undergoing screening*, that are currently not evaluated as part of the ProtecT treatment trial. Proposed new subgroups are: (a) non-attendees for PSA testing, (b) men with 'normal' (i.e <3.0ng/ml) PSA levels, (c) men with raised PSA levels who refuse biopsy, (d) men with negative biopsy and (e) men diagnosed with advanced cancer at screening. The framework for these subgroups is in Figure 1. In-depth interviews will be conducted with men in each of these subgroups to explore their perceptions and experiences of study information, interpretations of the risks and benefits of PSA testing and biopsy, perceptions of future risk of prostate cancer and the acceptability of their situation (Appendix A). Information will supplement quantitative HRQL data to improve understanding of self-reported health data and men's health beliefs and values. This information will also inform development of the health beliefs model (see below). Hypotheses and timings of HRQL assessments are outlined in Table 1.

Table 1 HRQL hypotheses and timing of assessments

Groups of men	Hypotheses	Instruments	Timings
(a) Non attendees	i) Compared to those attending for PSA testing, the majority of non-attendees have lower levels of anxiety and fewer urinary symptoms than attendees because of perceived 'healthy' state. ii) There will be a small group of non-attendees for PSA testing that have higher levels of anxiety and more urinary symptoms than attendees iii) Non-attendees have levels of sexual functioning similar to population norms (data will be compared with men treated for prostate cancer)	SF12, EQ-5D, HAD, UCLA & ICS	At refusal
(b) PSA < 3.0ng/ml	i) Men with PSA < 3.0 ng/ml have less anxiety than men with raised PSA awaiting a biopsy because of the reassuring result	SF12, EQ-5D, HAD	At result
(c) Refused biopsy	This complex group is at risk of developing cancer (at least 25% have it): i) Men have more anxiety (and psychosocial issues) than men agreeing to a biopsy because of fear of the test, fear of rare complications or fear of cancer. ii) Men have better general health scores because of the belief that they do not feel ill and do not have cancer	SF12, EQ-5D, HAD, UCLA & ICS	At refusal
(d) Negative biopsy	i) Less anxiety than men with positive biopsy related to reassuring result ii) Over time there is the potential for increased HRQL impact because of awareness of increased risk of cancer/false negative results and experience of repeated investigations including re-biopsy, PSA monitoring and the risk of developing clinically apparent prostate cancer.	SF12, EQ-5D, HAD	At result & 6 months
(e) Advanced cancer	i) Essential data to link into health economics model. ii) Men may have more symptoms, psychosocial issues and worse HRQL scores than men with localised disease because of risk of disease progression and ineligibility for curative treatment	SF12, EQ-5D, HAD, UCLA & ICS	At diagnosis & at 6 months

Assessments will be made within two weeks of notification of decision not to attend for PSA testing/refusal of biopsy or within a week of receiving results in an attempt to capture transient short-term effects of screening. Men consenting, who participate will be mailed questionnaires with a follow up telephone reminder if necessary. Reasons for choice of instrument are detailed below.

Choice of HRQL instruments

There are many studies and instruments measuring HRQL in men with early prostate cancer but HRQL assessments during *screening* studies are less common and no specific instruments for prostate cancer screening have been developed. A recent review of HRQL assessment in cancer screening studies found no consistency between questionnaires used between studies and the authors suggested that [7,15]validated general and symptom-specific health status instruments should be used in screening studies to ensure that clinically relevant outcomes are measured as well as outcomes of interest to the research question[16]. We intend to use similar measures to those in ERSPC studies (SF12, EQ-5D, modified UCLA & State/Trait Anxiety inventory) to allow pooling of data as well as comparative analyses to be performed[17]. Measures chosen for this study also are similar to instruments within the ProtecT treatment trial.

Generic health measures

The generic health status measure SF-12 has 12-items comparable with the SF-36, yet with the advantage of being easier and quicker to complete. It is reliable, valid and responsive to changes in health status. The 12 items form two key domains, physical and mental function. It has been well validated and normative population data are available for comparison[18]. It has been completed by men in the ProtecT trial from inception, and will be completed by all subgroups of men (Table 1).

Utilities

The EQ-5D is a generic health index that produces a utility score between 0 and 1[19]. It is easy to complete and provides data comparable across populations. Data will inform the Markov models developed by Wolstenholme et al, funded by CR UK. One model simulates the test part of the screening programme and the second model simulates progression from referral for treatment to death. These will produce results in the form of cost per life-year and cost per quality adjusted life year gained. It has been completed by men in the ProtecT trial from inception and will be completed by all subgroups of men (Table 1).

Anxiety and depression

The Hospital Anxiety and Depression scale (HAD) is a widely used tool for assessing psychological distress in patients and non-clinical groups and has been used in screening studies in breast cancer [16,20,21]. It consists of 14 items divided into two scales of anxiety and depression. Experience from the ERSPC studies indicate that although psychopathology related to screening is generally low, some men experience distressing symptoms and this tool is sensitive to these problems (personal communication Marie-Loiuse Essink-Bot). It has been completed by men in the ProtecT trial from inception, and will be completed by all subgroups of men (Table 1).

Disease specific issues

Assessment of lower urinary tract symptoms related to the development of benign prostatatic hypertrophy and impact of diagnostic tests, prostate cancer and treatment is important because men with more symptoms probably demonstrate different health behaviour to those who are asymptomatic and radical surgical or radiotherapy treatment for prostate cancer can cause incontinence and increased lower urinary tract symptoms, among other sequelae[13,14]. There are many validated tools available for this purpose. We intend to use the 20-item self-administered UCLA Prostate Cancer Index, parts of which are used within ERSPC studies. It is a reliable and valid tool that quantifies: urinary function and bother, sexual function and bother, and bowel function and bother[22]. Data from ERSPC studies indicate some problems with the UCLA sexual function scale, therefore scales will be supplemented by the International Continence Society (ICS) urinary symptoms and sexual function questionnaires[17,23-25]. Both

are self-administered questionnaires validated for measuring lower urinary tract symptoms and sexual function in middle-aged and elderly men in the UK, internationally, in the general population and in urology clinics [26-28]. The expanded UCLA scale (Expanded Prostate Index Composite) including a hormonal domain will be used in men developing advanced disease[29]. Disease specific HRQL issues will be assessed in subgroups (a), (c) and (e). Men who decline PSA testing (50%) or prostate biopsy (25%) may have specific urinary or sexual issues that influence health behaviours and men with advanced cancers (e) will experience deterioration in specific HRQL related to disease progression and to treatment.

Qualitative interviews

Qualitative research methods have been integral to the development and successful implementation of the ProtecT treatment trial[30]. In-depth interviews have been carried out with over 60 participants at a range of time points to explore men's perceptions and understandings of prostate cancer and the acceptability of randomisation and each of the treatments, as well as their interpretations of study information, and the experience of participation in the study. Interviews have explored views and beliefs about the risks and benefits of PSA testing, issues in screening and the need for a randomised trial of treatment. Data from these interviews will be extracted to inform the development of items to test the Health Belief Model, and to explore the meanings and relevance of the model to health behaviour and attitudes. As part of this proposal, additional in-depth interviews will be conducted with men in each of the subgroups a to e to explore experiences in each of these groups and supplement HRQL data.

In-depth interviews will be undertaken with approximately 10 individuals in each of the subgroups for initial study, and then purposive, theoretical sampling will be used to include, iteratively, additional individuals to provide a rounded and grounded understanding of the perspective of the subgroup under study. In some subgroups, 10 individuals may be sufficient to achieve saturation (where no new themes emerge from additional data collection), but in other subgroups double this number may be needed, and data collection will continue until saturation is reached. Interviews will be carried out by the trained named researcher and will be semi-structured, conducted using a checklist of topics to ensure similar aspects are covered in each interview, but encouraging other issues of importance to the men to emerge. All interviews will be fully transcribed and then coded to allow the emergence of the major themes associated with each of the subgroups. Analysis will be by constant comparison, involving detailed interrogation of the data by reading and re-reading transcripts and coded segments to identify cogent themes[31]. Sampling, interview technique, coding and analysis will be supervised and checked by JD and JM. The main purpose of the qualitative data will be to understand the perspectives of men in each of the subgroups, but the interviews and data gathered will also be used to inform the development of the health beliefs model, and to assist in the interpretation of the quantitative HRQL data.

Sample size calculation

In total, in the ProtecT trial, 115,000 men are expected to attend for PSA testing. Assuming that attendance rates continue as previously, then the expected numbers of men that will form each group during the one year data collection period (January to December 2005) is as follows: (a) 20,000, (b) 18,000, (c) 400, (d) 1,500 (e)50. These data are based on results from the first two years of the ProtecT study. Random samples will be invited to participate in the HRQL study from subgroups a), b), d). All men in subgroups (c) and (e) will be invited to participate.

Sample size calculations are based on HAD scale scores. Data from the ProtecT feasibility study indicated a mean HAD score of 5 (standard deviation 3.5) in this population for both anxiety and depression. Measurement of HRQL in studies where individuals are grouped at GP practice level has shown very little effect of clustering[32], and the average number of men per cluster will not greatly exceed 1 in each group. Therefore the "design effect" (the factor by which the sample size should be multiplied to allow for clustering) is likely to be close to 1, since design effect=1+(n-1)$\times$ICC, where n is the average number of men per cluster and ICC is the intraclass correlation coefficient.

Table 2 shows the number of men per group required to detect mean differences between HAD scores of between 1 and 1.4, with power of 80% and 90%, both with and without adjustment for clustering. It can be seen that differences as small as 1.0 can be detected with 80% power, even in the unlikely

context of a design effect as high as 1.25, provided that there are at least 241 men in each group. We conclude that a minimum of 250 men in each of groups a), b), c), and d) will provide reasonable power to examine between-group mean differences in HRQL.

Table 2 Number of men required per group to detect mean differences in HAD scores, assuming a standard deviation of 3.5 in each group, two-sided 5% significance levels

Mean difference detectable	Power = 80%		Power = 90%	
	Design effect = 1 (no clustering)	Design effect = 1.25	Design effect = 1 (no clustering)	Design effect = 1.25
1.4	99	124	132	165
1.2	134	168	179	224
1	193	241	258	323

Planned analyses

This statistical analysis plan is summarised in Table 3. For each of the hypotheses in Table 1, multiple linear regression will be used to estimate the mean difference in scores between groups for each HRQL measure in turn. This method allows the estimated mean difference between groups to be adjusted for demographic differences between those groups (all hypotheses), and for any difference in scores at the pre-PSA assessment of HRQL (hypotheses b to d). In all cases, unadjusted and adjusted mean differences will be presented. The strength of evidence for each mean difference in scores will be quantified as a 95% confidence interval and a p-value.

As measures of HRQL give scores on arbitrary scales the “effect size” will also be presented, this being the mean difference in scores divided by the pooled standard deviations of scores in the two groups. This extra statistic will allow easier comparison of the results of the current work with the results of other studies using other measures of HRQL. Hypotheses (dii) will be addressed using repeated measures of HRQL, around the time of biopsy and at 6 months. Differences in the change in HRQL over time, between groups of men, will be estimated by adding the interaction between assessment time and group to the multiple regression analysis. Estimation of standard errors will accommodate the correlations between repeated reports of HRQL by the men.

If, for a comparison, a number of men fail to provide HRQoL assessments, the primary analysis will be based upon the observed data. In addition, a sensitivity analysis will be conducted. Hypotheses will be made about why men did not respond, consistent responses imputed for them, and the analysis repeated. Ideally, this will demonstrate the robustness of the primary results to different possible reasons for non-response (e.g. worsening illness).

Table 3 Summary of the statistical analysis plan

Hypothesis	Comparisons	Planned analyses
(a-i) Compared to those attending for PSA testing, the majority of non-attendees have lower levels of anxiety and fewer symptoms because of perceived 'healthy' state	Groups (a) *vs.* (1)	Multiple regression with group & baseline demographics as covariates, anxiety as the outcome
(a-ii) There will be a small group of non-attendees for PSA testing that have higher levels of anxiety and more urinary symptoms than attendees	Those reporting physical symptoms in Groups (a) *vs.* (1).	Multiple regression with group, baseline demographics & physical symptoms as covariates, anxiety as the outcome
(b) Men with PSA < 3.0ng/ml have less anxiety than men with raised PSA	Groups (b) *vs.* (2) + (c)	Multiple regression with group & baseline demographics & anxiety as covariates, anxiety at PSA result as the outcome.
(c-i) Men report more anxiety/psychosocial issues than men agreeing to a biopsy	Groups (c) *vs.* (2)	Multiple regression with group & baseline demographics & anxiety as covariates, anxiety at PSA result as the outcome
(c-ii) Men have better general health scores because of the belief that they do not feel ill and do not have cancer	Groups (c) *vs.* (2)	Multiple regression with group & baseline demographics & HRQL as covariates, HRQL measure as the outcome
(d-i) Less anxiety than men with positive biopsy because of reassuring result	Groups (d) *vs.* (3)	Multiple regression with group & baseline demographics & anxiety as covariates, anxiety at biopsy result as the outcome
(d-ii) Over time there is potential for increased HRQL impact because of awareness of increased risk of cancer / false negative results.	Groups (d) *vs.* (3)	Multiple regression with group, time of assessment, group X time interaction, baseline demographics & HRQL as covariates, post-biopsy HRQL measure as outcome. Robust estimates of standard error
(e - ii) Men have more symptoms, psychosocial issues and worse HRQL scores	Groups (e) *vs.* (3)	Multiple regression with group & baseline demographics as covariates, HRQL measure as the outcome

A conceptual health behaviour model for predicting uptake of screening

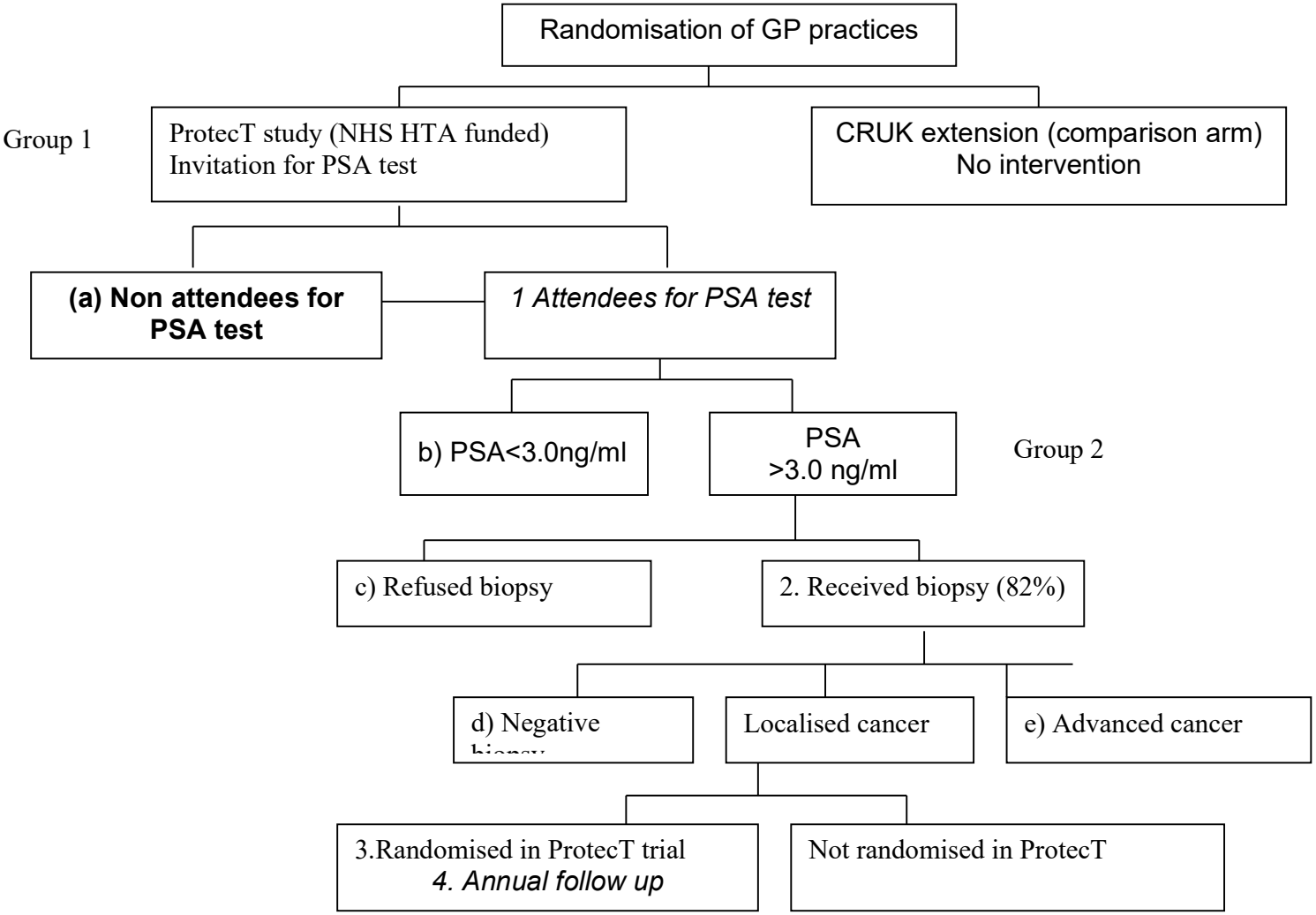
Identification of factors that influence uptake of screening and diagnostic testing in the study will be achieved using the theoretical framework afforded by the Health Belief Model[33]. This model focuses on six key determinants of health behaviours: beliefs regarding '*threat*', '*susceptibility*', '*severity*', '*benefits*', *'barriers'*, '*cues to action*' and '*general health motivation*'. The model has been used widely in the area of screening and has been shown to be effective in predicting the uptake of screening for many conditions including prostate cancer[34,35]. Furthermore, the model has been shown to be useful in the design of interventions to modify a range of health behaviours including screening uptake[36,37]. Other theoretical frameworks afforded by various health behaviour models, including the Theory of Planned Behaviour, Theory of Reasoned Action, Protection Motivation Theory, Social Cognitive Theory, Health Locus of Control and Self-Efficacy Theory, will also be considered. The Health Belief Model uses both qualitative and quantitative research methods[38]. Items will be generated with reference to the existing health belief model in the literature, evidence from the prostate cancer literature on patients' experiences of screening and after analysing semi-structured interviews that have been conducted with men in the ProtecT study. Men have been interviewed at each of the major steps of the pathway from screening to diagnosis in the ProtecT trial. The principle investigators of the ProtecT study will review this model to ensure it has face

validity and acceptability. This model will then be tested further using purposive sampling techniques in men who are considering PSA screening and men who decline a biopsy. We anticipate that this will involve some additional interviews in these subgroups (see above) to ensure that saturation is achieved. The results from the interviews will enable us to develop a quantitative measure of health beliefs. Two versions of this measure will be produced in order to capture (i) the determinants of screening attendance and (ii) the determinants of attendance for biopsy. This is essential as the issues involved in screening and biopsy will differ somewhat. Furthermore, men who are invited for biopsy will have additional information on their 'risk' status (compared with men who are invited for screening), because they will be aware of their PSA test result.

To establish the validity and reliability of the measures, the resultant scales will be distributed to a random sample of men in the Protect trial who are either considering (a) screening or (b) a biopsy. The sample size will be influenced by the number of items in the scale. We anticipate that, consistent with previous research, this sample will involve 250 respondents[39]. Analyses will be conducted to examine internal reliability and construct validity of each subscale. The results will enable us to undertake refinements to the scale. The finalised measure will then be distributed to two groups of men in the trial. First, to men who are invited to participate in screening. This will enable us to identify determinants that predict attendance for PSA testing. Second, to men who are identified as having an elevated PSA and are invited to biopsy. This will enable us to identify the determinants that predict agreement to biopsy.

Figure 1. Subgroups of men identified during ProtecT and CRUK funded extension

1 to 4 current HRQL assessments in italic
a to e subgroups for HRQL assessment and qualitative interviews in bold
Groups 1,2 health behaviour model questionnaires (pre-PSA and pre-biopsy)



Appendix A

Exemplar topic guides for qualitative interviews with subgroups of men in the extension of ProtecT HRQL study

1. All groups will cover these topics
i) General health/disease lay beliefs, particularly about cancer
- previous illness experience and family experience of cancer

ii) Knowledge/beliefs about prostate cancer:
- symptoms, prognosis, risk factors, prevalence, perception of personal risk

iii) Other concerns

2. Specific topics will be covered within each subgroup
Group (a), Non-attendees for PSA testing and Group (b), PSA < 3.0ng/ml
i) Reaction to invitation to test:
- initial reaction to screening invite,
- account of decision-making involved in declining/accepting offer
- involvement of significant others/family members
- consultation of additional information sources

ii) Beliefs about detection of prostate cancer by PSA test
- beliefs about screening/disease prevention
- beliefs about prostate cancer treatment

iii) Views about/understanding of the ProtecT study
- views about the questionnaires and study information
- views on the process of the prostate check clinic

Groups (c), men with PSA > 3.0ng/ml who refused a prostate biopsy and Group (d), men with PSA > 3.0ng/ml and a negative biopsy
i) Reaction to invitation to prostate biopsy /PSA result:
- account of initial reaction to prostate biopsy invite,
- account of decision-making involved in declining/accepting offer
- involvement of significant others/family members
- consultation of additional information sources

ii) Account of testing process (Group d)

iii) Beliefs about PSA and other tests performed
- appraisal of personal risks/benefits of treatment of prostate cancer

Group (e), men diagnosed with advanced prostate cancer
i) Understanding of the detailed diagnosis
- beliefs about signs/symptoms
- beliefs about prostate cancer causation
- account of personal 'coping'
- views about the future

- views of prostate cancer screening

ii) Experience of treatment/side effects

Reference List to Appendix 1

1. Roumier X, Azzouzi R, Valeri A, *et al*. Adherence to an annual PSA screening program over 3 years for brothers and sons of men with prostate cancer. *Euorpean Urology* 2004;**45**:280-6.

2. Zackrisson S, Andersson I, Manjer J, Janzon L. Non-attendance in breast cancer screening is associated with unfavourable socio-economic circumstances & advanced cancer. *Int J Cancer* 2004;**108**:754-60.

3. Jacobsen PB, Lamonde LA, Honour M, *et al*. Relation of family history of prostate cancer to perceived vulnerability and screening behavior. *Psycho-Oncology* 2004;**13**:80-5.

4. de Koning HJ, Auvinen A, Berenguer Sanchez A, *et al*. Large-scale randomized prostate cancer screening trials: program performances in the European randomized screening for prostate cancer trial and the prostate, lung, colorectal and ovary cancer trial. *Int J Cancer* 97, 237-244. 2002.

5. Hasson MA, Fagerstrom R, Kahane DC, *et al*. Design and evolution of the data management systems in the prostate, lung, colorectal and ovarian(PLCO) Cancer Screening Trial *Con Clin Trials* 2000;**21**:329-48S

6. Frankel S, Smith GD, Donovan J, Neal D. Screening for prostate cancer. *Lancet* 2003;**361**:1122-8.

7. Miller AB, Madalinska JB, Church T, *et al*. HRQL and cost-effectiveness studies in the European randomised study of screening for prostate cancer and the US PLCO trial. *Eur J Cancer* 2001;**37**:2154-60.

8. Schroder FH, Denis LJ, Roobol M. The story of the European randomized study of screening for prostate cancer. *Brit J Urol Int* 2003;**92**:1-13.

9. Essink-Bot ML, de Koning HJ, Nijs HG. Short-term effects of population-based screening for prostate cancer on health-related quality of life. *J Natl Cancer Inst* 1998;**90**:925-31.

10. Madalinska JB, Essink-Bot ML, de Koning HJ, *et al*. HRQL in patients with screen-detected versus clinically diagnosed prostate cancer preceding primary treatment. *Prostate* 2001;**46**:87-97.

11. Korfage IJ, Essink-Bot ML, Roobol MJ. The impact of prostate cancer diagnosis on mental health. Quality of Life Research 12, 858. 2003.

12. Madalinska J, Essink-Bot M, de Koning H. HRQL effects of radical prostatectomy & primary radiotherapy for screen-detected or clinically diagnosed localized prostate cancer. *J Clin Oncol* 2001;**19**:1619-28

13. Steinbeck G, Helgesen F, Adolfsson J, *et al*. Quality of Life After Radical Prostatectomy or Watchful Waiting. *N Engl J Med* 2002;**347**:790-6.

14. Nijs HGT, Essink-Bot ML, DeKoning HJ, Kirkels WJ, Schroder FH. Why do men refuse or attend opoulation -based screening for prostate cancer. *J Public Health Med* 2000;**22**:312-6.

15. Penson DF, Litwin MS, Aaronson NK. Health related quality of life in men with prostate cancer. *J Urol.* 2003;**169**:1653-61.

16. Velikova G, Booth L, Smith AB, *et al*. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. *J Clin Oncol* 2004;**22**:714-24.

17. Korfage IJ, Essink-Bot ML, Madalinska JB, *et al*. Measuring disease specific quality of life in localized prostate cancer: The Dutch experience. *Quality of Life Research* 2003;**12**:459-64.

18. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey - Construction of scales and preliminary tests of reliability and validity. *Medical Care* 1996;**34**:220-33.

19. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;**37**:53-72.

20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavia* 1983;**67**:361-70.

21. Lampic C, Thurfjell E, Bergh J, Sjoden PO. Short- and long-term anxiety and depression in women recalled after breast cancer screening. *European Journal of Cancer* 2001;**37**:463-9.

22. Litwin MS, Hays RD, Fink A, *et al*. The UCLA Prostate Cancer Index: Development, reliability and validity of a health-related quality of life measure. *Med Care* 1998;**36**:1002-12.

23. Donovan JL, Abrams P, Peters TJ, *et al*. The ICS-'BPH' Study: the psychometric validity and reliability of the ICSmale questionnaire. *British Journal of Urology* 1996;**77**:554-62.

24. Donovan JL, Peters TJ, Abrams P, *et al*. Scoring the short form ICSMALESF Questionnaire. *The Journal of Urology* 2000;**164**:1948-55.

25. Donovan JL, Kay HE, Peters TJ, *et al*. Using ICSQoL to measure the impact of lower urinary tract symptoms on quality of life: evidence from the ICS-'BPH' study. *Brit J Urology* 1997;**80**:712-21.

26. Frankel SJ, Donovan JL, Peters TJ, *et al*. Sexual dysfunction in men with lower urinary tract symptoms. *J Clin Epidemiol* 1998;**51(8)**:677-85.

27. Brookes ST, Donovan JL, Peters TJ, *et al*. Sexual dysfunction in men after treatment for lower urinary tract symptoms: evidence from randomised controlled trial. *BMJ* 2002;**324**:1059-64.

28. Brookes ST, Donovan JL, Peters TJ, *et al*. Sexual dysfunction in men after treatment for lower urinary tract symptoms: evidence from randomised controlled trial. *BMJ* 2002;**324**:1059-64.

29. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the expanded prostate cancer index compostie (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology* 2000;**56**:899-905.

30. Donovan J, Mills N, Smith M, *et al*. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT study. *BMJ* 2002;**325**:766-70.

31. Hammersley M, Atkinson P. Ethnography. London: Tavistock, 1983.

32. Premaratne UN, Sterne JA, Marks GB, Webb J, Burney PG. Evaluation of a community intervention to improve the management of asthma: The Greenwich Asthma Study. 1998.

33. Becker MH, Maiman LA, Kirscht JP, Haefner DP, Drachman RH. The health belief model and prediction of dietary compliance field experiment. *J Health Soc Behav* 1977;**18** :348-66.

34. Wardle J, Sutton S, Williamson S, *et al*. Psychosocial influences on older adults' interest in participating in bowel cancer screening. *Preventive Medicine* 2000;**31**:323-34.

35. Finney Rutten LJ, Iannotti RJ. Health beliefs, salience of breast cancer family history, and involvement with breast cancer issues: adherence to annual mammography screening recommendations. *Cancer Detection and Prevention* 2003;**27**:353-9.

36. Fox SA, Stein JA, Sockloskie RJ, Ory MG. Targeted mailed materials and the medicare beneficiary: Increasing mammogram screening among the elderly. *Am J Public Health* 2001;**91**:55-61.

37. Abood DA, Black DR, Feral D. Nutrition education worksite intervention for university staff: Application of the Health Belief Model. *Journal of Nutrition Education & Behaviour* 2003;**35**:260-7.

38. Conner, M, Norman, P. Predicting health behaviour. 1995. Open University Press, Buckingham UK.

Champion VL. Instrument development for health belief model constructs. *Advances in Nursing Science* 1984;**6**:73-85.

Appendix 2

Procedure for obtaining GP lists

Background

The aim of this procedure is to ensure that the same calendar period is covered by follow-up of the **ProtecT** and **CAP** practices in each cluster.

It is assumed that statistical analysis of the resulting data will be by a method which explicitly incorporates any changing incidence over time. Event time analysis using Cox's proportional hazards regression would be one way of achieving this. For such analyses it is sufficient that follow-up in the groups to be compared is over the same time period, with no need for a balance in person-years of follow-up during the different calendar periods between the two studies.

The procedure

[1] For a given cluster note the earliest date (referred to below as date E) during which a practice list was obtained for a **ProtecT** practice.

[2] If no lists have been obtained for **ProtecT** practices, or no list was obtained more than 6 months ago, obtain the current practice lists for **CAP** practices in that cluster.

[3] If, for **ProtecT** practices in the cluster, one or more lists were obtained more than 6 months ago, then attempt to obtain a retrospective list for each **CAP** practice consenting to take part until two retrospective practice lists have been obtained for date E.

- Retrospective lists should be obtained for date E if possible.

- If two or more **CAP** practices in a cluster are awaiting the retrieval of their lists then the order in which they are approached must be randomised. Contact Chris Metcalfe for a randomised order.

- If, for a practice, a retrospective list can only be obtained for a date more recent than date E, then obtain a retrospective list for that more recent date. This practice does not contribute to the target of two retrospective practice lists for date E.

- If a retrospective list cannot be obtained at all, obtain the current practice list.

Once two retrospective lists for date E have been obtained, then obtain current practice lists for subsequently consenting **CAP** practices in the cluster. There is no longer a need to randomise the order of approaching practices for that cluster.

Footnote

Where the date of having obtained a list from a **ProtecT** practice is not available, then estimate from the dates at which men were invited to attend for PSA testing.

Summary of Protocol Approvals & Amendments

<table>
<tr><td colspan="2">Title: CAP Trial
<u>C</u>luster randomised tri<u>A</u>l of PSA testing for <u>P</u>rostate cancer
(previously <u>C</u>omparison <u>A</u>rm to <u>P</u>rotect Study).</td></tr>
<tr><td>Sponsor: University of Bristol

Funding: Cancer Research UK & The Department of Health C11043/A4286, C18281/A8145, C18281/A11326, C18281/A15064, C18281_A24432</td><td>Ethics: Derby National Research Ethics Service Committee East Midlands, formerly Trent Multi-centre Research Ethics Committee).

<u>MREC/03/4/093</u>: Evaluating population-based screening for localised prostate cancer in the United Kingdom – an extension to the ProtecT treatment trial. Part 1 – Flagging.

<u>05/MRE04/78</u>: Evaluating population-based screening for localised prostate cancer in the United Kingdom – an extension to the ProtecT treatment trial; application for case-note review.

PIAG 4-09 (k)/2003: Approval for the flagging of men in the control group & non-responders in the intervention group under Section 251 of the NHS Act 2006 (UK Patient Information Advisory Group (PIAG), now the Confidentiality Group (CAG)).

PIAG 1-05(f)/2006: Approval for the review of medical records of men who died of a cause potentially related to prostate cancer before consent could be obtained (provided the man did not record an objection to their medical records being used for research whilst alive).

MREC/01/4/025: Approval for taking individual informed consent for intervention group men attending the prostate check clinic.</td></tr>
<tr><td>ISRCTN 92187251</td><td>Principal Investigators: Professor RM Martin (University of Bristol), Professor JL Donovan (University of Bristol), Professor FC Hamdy (University of Oxford) and Professor DE Neal (University of Cambridge).
Trial Co-ordinator: Dr Emma Turner (University of Bristol).</td></tr>
</table>

	Protocol v1.0 (Aug 2003) – *working document* [MREC approved 12 Feb 2004] Protocol v2.0 (June 2004) – *working document* [No MREC approval] **[First Protocol with FINAL study design, Version 3]** Protocol v3.0 (Sept 2005) – MREC approved 24 Nov 2005 Protocol v4.0 (15 Aug 2006) – MREC approved 18 Oct 2006 Protocol v5.0 (16 July 2007) – MREC approved 10 Sept 2007 Protocol v6.0 (09 Dec 2010) – MREC approved 07 Jan 2011 Protocol v7.0 (29 May 2012) – MREC approved 11 Jun 2012 Protocol v8.0 (20 Dec 2016) – MREC approved 25 Jan 2017 Protocol v9.0 (21 Oct 2021) – MREC approved 16th Nov 2021

Ethics Approvals and List of Amendments

Amendment No.	Application Date	Approval Date	Amendment Title & Documents Submitted
MREC/03/4/093 Initial Application	29 Jan 2004	**12 Feb 2004** Approval under Section C of the DoH "No local researcher" guidelines	**Evaluating population-based screening for localised prostate cancer in the United Kingdom – an extension to the ProtecT treatment trial. Part 1 – Flagging** Application form (29/01/2004) GP information sheet for Protect Study v2 (05/01/2004) GP information Sheet – Comparison arm v2 (09/01/2004) Consent form v1 (Feb 2002) Protocol v1 (Aug 2003) Flow chart of Study v1 (11/08/2003) Notice for patients v1 (Jan 2004) PIAG letter of approval – flagging (18 Dec 2003) Peer review and funding information Data Safety Committee members Method of initial recruitment to study Payments to researcher Provision of expenses for subjects Compensation arrangements for subjects Indemnity for investigators Chief investigators CV – Professor Jenny Linda Donovan

05/MRE04/78 Initial Application	19 Sept 2005 (further info submitted 26 Oct 2005)	**24 Nov 2005** Study designated as "exempt from site-specific assessment".	**Evaluating population-based screening for localised prostate cancer in the United Kingdom – an extension to the ProtecT treatment trial; application for case-note review** Application (19 Sept 2005) Investigator CV Protocol v3 (Sept 2005) **[First Protocol with FINAL study design]** Letter from Sponsor (13 Aug 2004) Compensation arrangements – letter from UoB (06/09/2005) Patient invitation letter (GP) v1 (15/09/2006) 2nd patient invitation letter (GP) v1 (15/09/2006) Patient invitation letter (cons) v1 (15/09/2006) 2nd patient invitation letter (cons) v1 (15/09/2006) GP letter and consent form v1 (15/09/2006) 2nd GP letter and consent form v1 (15/09/2006) GP (other) letter and consent form v1 (15/09/2006) 2nd GP (other) letter and consent form v1 (15/09/2006) Cons letter & consent (Protect) v1 (15/09/2006) 2nd cons letter & consent (Protect) v1 (15/09/2006) Cons letter & consent (non-Protect) v1 (15/09/2006) 2nd cons letter & consent (non-Protect) v1 (15/09/2006) Participant information sheet (GP) v2 (19/10/2005) Participant information sheet (cons) v2 (19/10/2005) Partic info sheet (cons), letter & consent (Protect) v1 (15/09/2005) Participant consent form v1 (15/09/2005) Patient consent form (cons) v1 (15/09/2005) Response to request for further information (26/10/2005) Protocol for determining cause of death, v2 (24/10/2005) Letter from Cancer Research UK (04/11/2003) Data extraction proforma v2 (23/05/2005)
MREC/03/4/093 Amendment 1	26 Sept 2006	**18 Oct 2006**	**Extension of Recruitment Period: Introduction of contamination study** Notice of substantial amendment (26/09/2006) CAP protocol v4 (Aug 2006) GP letter for ad hoc testing study v1 (06/07/2006) CAP acknowledgement letter v1 (15/08/2006) Protect acknowledgment letter v1 (15/08/2006) GP refusal letter v1 (17/08/2006) GP information sheet comparison v4 (17/08/2006) GP information sheet Protect v4 (17/08/2006) Notice for patients v2 (26/04/2006)
05/MRE04/78 Amendment 1	26 Sept 2006	**18 Oct 2006**	Notice of substantial amendment (26/09/2006) CAP protocol v4 (Aug 2006) GP letter & consent form next of kin v1 (17/08/2006) Next of kin letter v1 (17/08/2006) Patient invitation letter (GP no contact) v1 (26/04/2006) Patient information sheet (GP no contact) v1 (26/04/2006) Patient consent form (GP no contact) v1 (26/04/2006) Appointment cover letter to GP or nurse v1 (09/03/2006) Appointment feedback form v1 (09/03/2006) Cons letter and consent (Protect) v2 (08/08/2006) Cons letter and consent (non-Protect) v2 (08/08/2006) 2nd cons letter and consent (Protect) v2 (08/08/2006) 2nd cons letter and consent (non-Protect) v2 (08/08/2006) Patient invitation letter (GP) v2 (26/04/2006) Patient invitation letter (cons) v2 (26/04/2006) 2nd patient invitation letter (GP) v2 (26/04/2006) 2nd patient invitation letter (cons) v2 (26/04/2006) Patient information sheet (GP) v3 (26/04/2006) Patient information sheet (cons) v3 (26/04/2006) Patient consent form (GP) v2 (26/04/2006) Patient consent form (cons) v2 (26/04/2006)

			PIAG letter (20/03/2006)
MREC/03/4/093A mendment 2	28 Sept 2006	**18 Oct 2006**	**Change of CI to Dr Richard Martin** Notification of amendment (28/09/2006) CV for Richard Martin
05/MRE04/78 Amendment 2	28 Sept 2006	**18 Oct 2006**	**Change of CI to Dr Richard Martin** Notification of amendment (28/09/2006) CV for Richard Martin
MREC/03/4/093A mendment 3	25 Jun 2007	**10 Sept 2007**	Notice of substantial amendment (30/07/2007) GP refusal letter v2 (16/07/2007) GP information sheet comparison v5 (16/07/2007) Newsletter for GPs overall figures v1 (17/07/2007) CAP protocol v5 (16/07/2007) **NB - Approval letter re-issued 14 Nov 2007 to correct list of approved documents**
05/MRE04/78 Amendment 3	25 Jun 2007	**10 Sept 2007**	Notice of substantial amendment 3 (25/06/2007) Covering letter (01/08/2007) Protocol v5 (16/07/2007) Participant consent form, Consultant consent form v3 (23/07/2007) Participant consent form, GP consent form v3 (23/07/2007) Partic consent form, GP consent form (no contact) v2 (23/07/2007) GP letter and consent form (Dec), v1 (17/07/2007) GP (Other) letter and consent form (Dec), v1 (17/07/2007) 2nd patient invitation letter (GP) v2 (16/07/2007) 2nd patient invitation letter (cons) v2 (16/07/2007)
NB - No Amdt 4 **MREC/03/4/093 Amendment 5** (Labelled on paperwork as Amendment 1)	14 Dec 2010	**07 Jan 2011**	Protocol v6 (09/12/2010) Notice of substantial amendment (14/12/2010)
NB - No Amdt 4. **05/MRE04/78 Amendment 5** (Labelled on paperwork as Amendment 2)	14 Dec 2010	**07 Jan 2011**	Notice of substantial amendment (14/12/2010) Protocol v6 (09/12/2010) Letter of invitation to participant v2.2 (02/11/2010) GP/Consultant Information sheets v1 (03/11/2010) Incomplete patient consent letter v1 (01/06/2009) National spine – summary care record SOP, v1.1 (22/10/2010)
MREC/03/4/093 Amendment 6	31 May 2012	**11 June 2012**	Protocol v7 (29/05/2012) Notice of substantial amendment (31/05/2012)
05/MRE04/78 Amendment 6	31 May 2012	**11 June 2012**	Notice of substantial amendment 6 (31/05/2012) Protocol v7 (29/05/2012) Participant information sheet (GP) v 3.2 (18/05/2012) Partic consent form: PCT letter and consent form v1 (19/05/2012) Letter of invitation to participant (cons-alternative) v1 (20/12/2011) National Spine Summary care record SOP, v1.2 (18/05/2012)
MREC/03/4/093 Amendment 7	18 Nov 2015	**03 Dec 2015**	Notice of substantial amendment (18/11/2015) Notice for patients) v4 (23/09/2015) Participant information sheet (PIS) [GP] v4 (28/09/2015) Participant information sheet (PIS) [cons] v4 (28/09/2015)
05/MRE04/78 Amendment 7	17 Nov 2015	**21 Dec 2015**	Notice of substantial amendment 7 (17/11/2015) Other (Notice for patients) v4 (23/09/2015) Participant information sheet (PIS) [GP] v4 (28/09/2015) Participant information sheet (PIS) [cons] v4 (28/09/2015)
MREC/03/4/093 Amendment 8	02 Dec 2015	**04 Feb 2016**	Notice of substantial amendment 8 (02/12/2015) **Ethics numbers MREC/03/4/093 and 05/MRE04/78 combined**

MREC/03/4/093 Amendment 9	22 Dec 2016	**25 Jan 2017**	Covering letter on headed paper (21/12/2016) Notice of substantial amendment 9 (22/12/2016) Notice for patients (clean) v5 (28/07/2016) Notice for patients (tracked) v5 (28/07/2016) PIAG final approval (20/09/2016) Patient information sheet (clean) v5 (28/07/2016) Patient information sheet (tracked) v5 (28/07/2016) Patient information sheet (GP no contact) (clean) v2 (28/07/2016) Patient information sheet (GP no contact) (tracked) v2 (28/07/2016) Patient information sheet (GP) (clean) v5 (28/07/2016) Patient information sheet (GP) (tracked) v5 (28/07/2016) Protocol v8 (clean) (20/12/2016) Protocol v8 (tracked) (20/07/2016)
MREC/03/4/093 Amendment 10	31 Mar 2017	**3rd Apr 2017**	Non substantial amendment - Change of PI at Bristol, Cambridge, Newcastle and Cardiff Bristol - David Gillatt to Ed Rowe Cambridge – Andrew Doble to Vincent Gnanapragasm Newcastle – Philip Powell to Edgar Paez Cardiff – Howard Kynaston to Owen Highes
IRAS 196036 Amendment 11	4th Oct 20017	**13th Oct 2017**	Non substantial amendment – Notification of funding extension C18281_A24432_CAP grant award letter (16/05/2017)
IRAS 196036 Amendment 12	30 Aug 2019	**11th Sept 2019**	Non substantial amendment CAP NewsletterUpdated_20190724_v1 (24/07/2019)
IRAS 196036 Amendment 13	8th April 2020	**9th April 2020**	Non substantial amendment – suspension of trial fieldwork (COVID-19)
IRAS 196036 Amendment 14	28th Sept 2020	**28th Sept 2020**	Non substantial amendment – restarting trial fieldwork (following COVID-19 related halt)
IRAS 196036 Amendment 15	25th Oct 2021	**16th Nov 2021**	Substantial amendment CRUK_PPRC_2017_Letter of Offer_ 20210621 (15/06/2021) CRUK_PPRC_2017_Application_no cost extension (17/05/2021) CAP_protocol_v9_post 10 yr_2020CLEAN (21/10/2021) CAP_protocol_V9_post 10 yr_2020TRACKED (21/10/2021)

Bristol Randomised Trials Collaboration (BRTC)

CAP: Cluster randomised trial of testing for prostate cancer

Statistical Analysis Plan

Version 1.3 (16th December 2013)

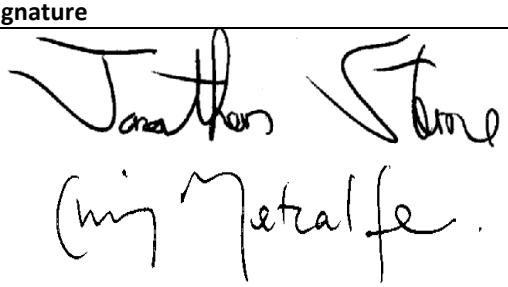
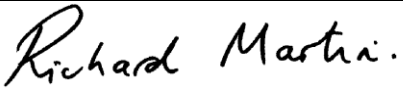
The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents			
Name	**Role**	**Signature**	**Date**
Chris Metcalfe & Jonathan Sterne	Author		24 Jan 2014
Simon Thompson	DMC statistician		18 Dec 2013
Richard Martin	Chief Investigator		24 Jan 2014

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)
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.

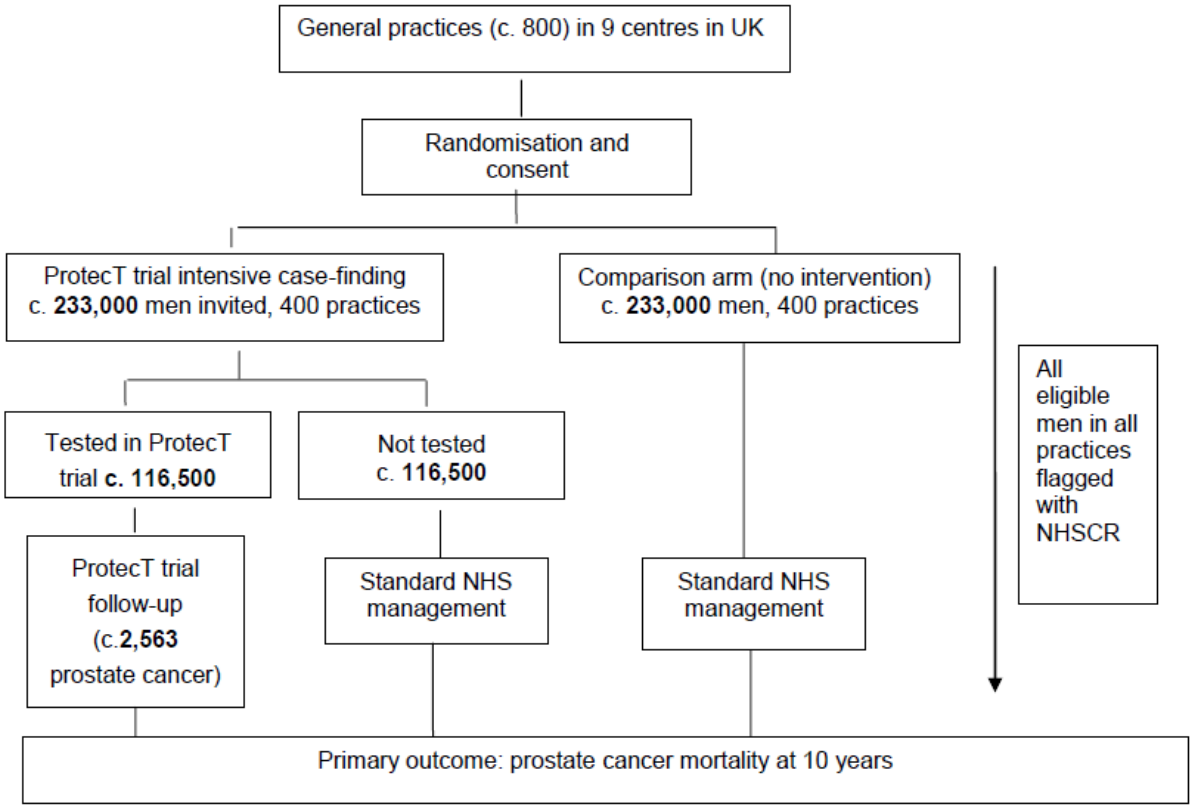
2.1. Trial aims and objectives

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 p**atient vignettes, prepared** to obsc**ure the study arm the patient i**s 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 be 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 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) 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,…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 (Metcalfe, 2013).

REFERENCES

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.

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

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. Screening and prostate cancer mortality in a randomized European study. New England Journal of Medicine 360:1320-8.

Bristol Randomised Trials Collaboration (BRTC)

CAP: Cluster randomised trial of PSA testing for prostate cancer

Statistical Analysis Plan

Version 1.5 (26th July 2016)

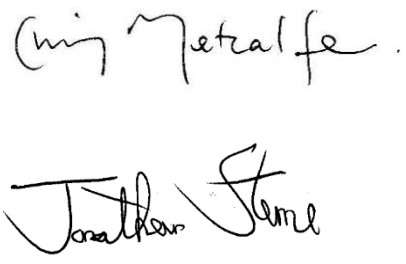
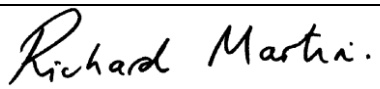
The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents			
Name	**Role**	**Signature**	**Date**
Chris Metcalfe & Jonathan Sterne	Author		19/08/2016
Simon Thompson	DMC statistician		26/08/2016
Richard Martin	Chief Investigator		31/08/2016

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)
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.

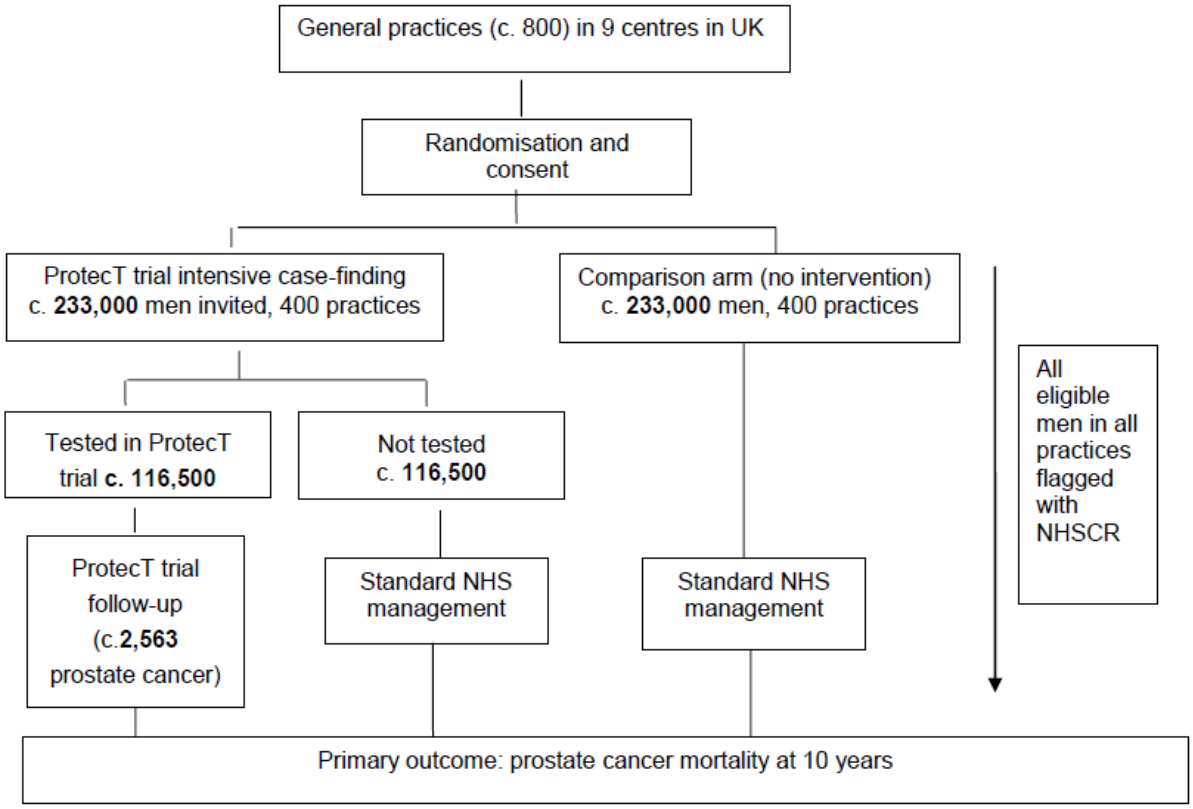
2.1. Trial aims and objectives

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

SAP Documents and Changes

Title: CAP Trial

Cluster randomised triAl of PSA testing for Prostate cancer

(previously Comparison Arm to Protect Study).

Version No.	Signed Date	Amendment Title & Documents Submitted
1.0 **Working Document**	**N/A**	**Working document for C. Metcalfe**
1.1 **Working Document**	**N/A**	**Working Document for C. Metcalfe**
1.2 **Working Document**	**N/A**	**Working Document for C. Metcalfe**
1.3	**24th Jan 2014**	**Original SAP**
1.4	**21st Nov 2014**	Changes since the previous version have been highlighted in green. In summary these are: • The calendar dates for the close of follow-up for the primary analysis have been added to Section 2.10.1 • On the advice of the Trial Steering Committee (January 2014), if there is evidence of a difference between study arms, we will present the number needed to screen, and the number needed to invite, as described in Section 6.2. • We previously planned to present, as a sensitivity analysis, an unbiased estimate of the effect of screening in those undergoing a study PSA test. On the advice of the Trial Steering Committee (January 2014), we will now present this as a secondary analysis, and consequently have pre-specified this analysis in more detail in Section 6.4. • 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 revised the categories of stage and grade in line with what we will be able to obtain. • The data available from Scotland and an outline of the planned analysis of those data are described in Section 6.8. • Outlines of the Figures and Tables to be included in the primary results paper are given in the Appendix.

1.5	**31st Aug 2016**	Substantive changes since version 1.3 have been highlighted in green, in several cases these changes represent further detail on changes introduced in version 1.4. In summary these are: • On the advice of the Trial Steering Committee (January 2016, see Appendix 2), if there is evidence of a difference between study arms, 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 updated on advice from Trial Steering Committee.