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Latest results from the UK trials evaluating prostate cancer screening and treatment: The CAP and ProtecT studies

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ABSTRACT

The European Randomised Study of Screening for Prostate Cancer (ERSPC) demonstrated a significant reduction in prostate cancer-specific mortality. The ongoing Comparison Arm for ProtecT (CAP) cluster randomised controlled trial (RCT) evaluates prostate cancer screening effectiveness by comparing primary care centres allocated to a round of prostate specific antigen (PSA) testing (intervention) or standard clinical care. Over 550 centres (around 450,000 men) were randomised in eight United Kingdom areas (2002–2008). Intervention group participants were also eligible for the ProtecT (Prostate testing for cancer and Treatment) RCT evaluating active monitoring, radiotherapy and radical prostatectomy treatments for localised prostate cancer. In ProtecT, over 1500 of around 3000 men with prostate cancer were randomised from over 10,000 with an elevated PSA in around 111,000 attendees at clinics. Investigation of the psychological impact of screening in a sub-sample showed that 10% of men still experienced high distress up to 3 months following prostate biopsies (22/227), although most were relatively unaffected. The risk of prostate cancer with a raised PSA was lower if urinary symptoms were present (frequent nocturia odds ratio (OR) 0.44, 95% confidence interval (CI) 0.22–0.83) or if a repeat PSA decreased by $\geqslant$20% prior to biopsy (OR 0.43, 95% CI 0.35–0.52). Men aged 45–49 years attended PSA clinics less frequently (442/1299, 34%) in a nested cohort with a cancer detection rate of 2.3% (10/442). The CAP and ProtecT trials (ISRCTN92187251 and ISRCTN20141217) will help resolve the prostate cancer screening debate, define the optimum treatment for localised disease and generate evidence to improve men's health.

1. Introduction

The merits of screening for prostate cancer and the most effective treatment for localised disease are amongst the most debated topics in contemporary health care. Recent publication of two randomised controlled trials (RCTs) of screening[1,2] has heightened the controversy. Despite a beneficial effect on disease-specific survival being demonstrated by the European Randomised Study of Screening for Prostate Cancer (ERSPC) unresolved issues remain regarding the magnitude of the screening benefit in different populations, the extent of over-diagnosis and over-treatment of low risk disease, the optimum treatment for localised disease and the costs of these policies. Answers to these key questions will

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influence screening and treatment policies for prostate cancer worldwide and in some countries, including the United Kingdom (UK), universal screening for prostate cancer is not currently advocated due to these uncertainties.

Two ongoing UK-based prostate cancer trials will help address these screening and treatment dilemmas. The CAP (Comparison Arm for ProtecT) study aims to evaluate the population effectiveness of prostate cancer screening using cluster randomisation of primary care centres to either prostate specific antigen testing (PSA) or to standard clinical care. The ProtecT (Prostate testing for cancer and Treatment) trial compares active monitoring, conformal external beam radiotherapy and radical prostatectomy treatments for clinically localised prostate cancer in individuals at centres randomised to PSA testing in the CAP trial. These two trials have primary outcomes of prostate cancer-specific mortality (including intervention-related mortality) measured at 10 years with secondary outcomes of overall survival, costs and quality of life.

This article outlines the designs of the CAP and ProtecT trials, summarises some latest findings and considers issues that will be resolved following the main trial publications in 2016.

2. Methods

2.1. CAP trial design

Primary care centres (general practices) located in and surrounding eight UK cities were randomised in clusters either to an intervention group comprising a single round of PSA testing (ProtecT protocol described below) or to a comparison group (Fig. 1) that received the UK NHS Prostate Cancer Risk Management advice (described in http://www.cancerscreening.nhs.uk/prostate/pcrm-aim.html). The National Health Service Information Centre (NHSIC) and regional cancer registries received details of all men aged 50–69 years without diagnosed prostate cancer at randomisation and provided regular notification of subsequent prostate cancer diagnoses or death. Clinical and resource use data were abstracted from medical records by trial staff following notification. Utilising the ERSPC[3] and Prostate, Lung, Colorectal and Ovarian (PLCO)[2] screening trial methods, a central committee (blind to trial allocation) received abstracted clinical data to review all deaths possibly due to prostate cancer or its treatment to avoid misattribution from death certificate information.[3]

The CAP and ProtecT trial primary outcomes are prostate cancer or intervention-related specific mortality at an average of 10 years following randomisation. Based on a calculation that accommodated contemporary age-specific UK prostate cancer diagnosis and mortality rates, clustering of men within primary care centres, the expected uptake of PSA testing in the intervention arm, and the expected contamination rate of PSA testing in the comparison arm, the CAP study sample size target was predicted to have 80% power to detect a 13% reduction in the odds of prostate cancer mortality in the intervention arm.

The trial was approved by the multi-centre research ethics committee (Trent MREC 03/4/093, 05/04/78) and the National Information Governance Board gave permission for data transfer to the NHSIC. An independent Data Monitoring Committee (DMC) oversees the CAP trial (ISRCTN92187251). A Trial Steering Committee with an independent chairman and members monitors the conduct and progress of both trials.

2.2. ProtecT trial design

A feasibility study established the recruitment methods and main trial design.[4] In the main trial, men aged 50–69 years

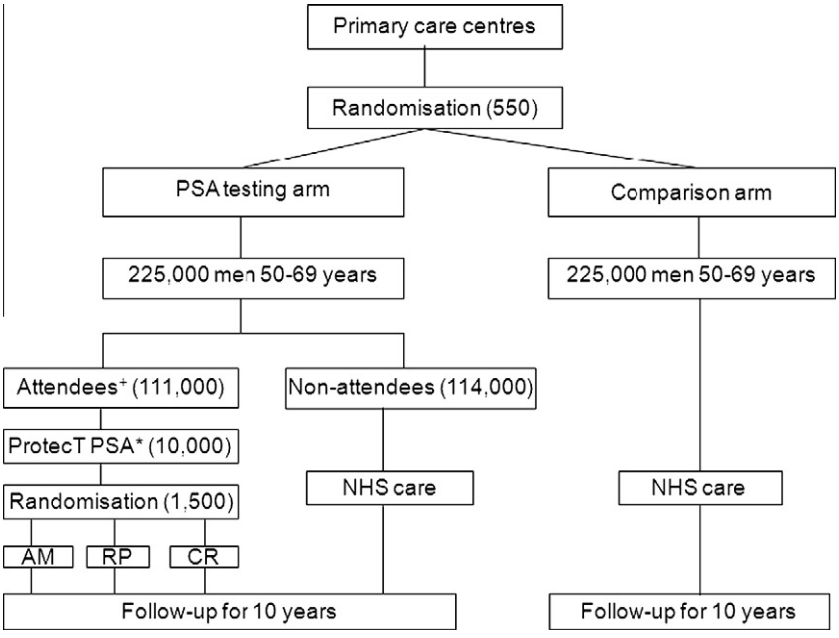

Fig. 1 – Flowchart of the comparison arm for ProtecT trial. All figures subjected to rounding. +Includes some attendees not in the CAP trial; *PSA result of 3.0 ng/ml or above; AM = active monitoring; RP = radical prostatectomy; CR = conformal radiotherapy; and NHS = National Health Service.

registered at CAP intervention practices were invited by letter. Men who attended the ProtecT recruitment clinics had the risks and benefits of a PSA test and participation in the study explained by trial nurses ('attendees')[4] (Fig. 1). If men participated in the study, serum was taken and a second consent form was completed subsequently to authorise PSA test processing. Participants with circulating PSA levels between 3 and 19.9 ng/ml were offered prostate biopsies at the clinical centres (10-core standardised procedure guided by transrectal ultrasound scans), a repeat PSA test and a digital rectal examination. Clinical centres were led by a urologist and a senior research nurse and trial appointments were largely nurse-led. Participants diagnosed with clinically localised prostate cancer were offered randomisation to conformal external beam radiotherapy, radical prostatectomy or active monitoring (regular assessment of PSA levels and disease status). Participants excluded from randomisation (for example those with advanced disease) received NHS care. All participants eligible for randomisation received trial follow-up under the comprehensive cohort principle. Multi-centre research ethics committee approval was obtained (Trent MREC01/4/025) and participants provided written informed consent. An independent DMC oversees the trial (ISRCTN20141217).

Socio-demographical, epidemiological and clinical factors such as disease family history and behaviour over the life-course were collected by research nurses and in questionnaires completed by all ProtecT participants at trial entry and by the comprehensive cohort 1 year later. Generic health, bowel and urinary symptoms, sexual function and mood questionnaires were completed by all ProtecT participants at trial entry, at biopsy and annually in the comprehensive cohort. At baseline, height and weight were measured and blood samples (whole blood, plasma and serum) taken with biopsy and prostatectomy tissue where relevant. Samples were biobanked for the translational Prostate Mechanisms of Progression and Treatment research study.

3. Results

3.1. CAP and ProtecT trial progress

Over 550 primary care centres participated in the CAP trial between 2002 and 2008 (Fig. 1) and the NHSIC has been notified of over 450,000 men. The CAP trial encompasses about 8% of the total male population aged 50–69 years in England and Wales. Recruitment to the ProtecT trial commenced in three centres in 1999, increased to nine in 2002 and was completed in 2008 with around 111,000 attendees at the recruitment clinics. There were over 10,000 ProtecT participants with a raised PSA (11%) and about 3000 were diagnosed with prostate cancer, of which around 400 had advanced disease (12%). Over 1500 participants with localised disease agreed to randomisation (63% of those eligible) with annual follow-up of these men at over 90%. An overview of recent publications from these trials is summarised according to the research focus.

3.2. Aetiology of prostate cancer

Aetiological research has focused on the metabolic and nutritional factors affecting prostate cancer risk, notably the vitamins A, D and E, the folate metabolic pathway[5] and diabetes.[6] The importance of insulin-like growth factor (IGF)[7,8] has been highlighted, including the possibility that IGFs and related binding proteins mediate early life exposures that subsequently influence adult height and prostate cancer risk.[9] In recent results, the inverse relationship between prostate cancer risk and diabetes was confirmed in over 1000 ProtecT participants with cancer and 6000 controls (odds ratio (OR) 0.78, 95% confidence interval (CI) 0.61–0.99).[6]

3.3. Genome-wide association studies (GWAS)

GWAS is a powerful technique that utilises the International HapMap Project (a human genetic variation dataset) and tag-SNPs (single-nucleotide polymorphisms) to identify common alleles that predispose to disease in individuals. The ProtecT study has underpinned an international GWAS in which participants at very low risk of prostate cancer (PSA < 0.5 ng/ml) were compared to men with prostate cancer diagnosed either at an early age or with a family history of the disease. Several new sites linked to prostate cancer risk were identified, including KLK2/3, MSMB and LMTK2.[10,11]

3.4. Psychological impact of prostate cancer screening and detection

The psychosocial impact of cancer screening and detection has been investigated extensively utilising questionnaire measures of mental health (SF-12), anxiety and depression (Hospital Anxiety and Depression scales) and participant interviews. There were no substantive differences in these measures between the PSA testing and biopsy stages neither in a sub-sample of nearly 5000 men,[12] nor between men accepting or refusing these tests.[13] Knowledge of established prostate cancer risk factors (PSA value, age and family history of the disease) also did not heighten men's anxiety preceding a biopsy in a sample of 4198 men.[14] Interviews confirmed that most men found the detection process routine and acceptable regardless of the final outcome.[15] However, those men interviewed who had refused screening tests were often anxious about the biopsy process or perceived that they had a low risk of disease, based on the absence of urinary symptoms. The HADs and SF-12 measures can be relatively insensitive in population-based settings so specific mood measures (Profile of Mood States) and a prostate cancer-specific anxiety/distress instrument (Impact of Events scale) were added subsequently to the ProtecT trial. Longitudinal assessments with these specific measures in a sub-sample of participants showed that levels of distress were greatest immediately prior to biopsy and affected 19% of men (33/171) although the majority of men were not greatly affected psychologically by PSA testing, biopsies or a negative biopsy result. However, 10% (22/227) of men reported high distress and a tense/anxious mood which persisted up to 12 weeks after a negative biopsy result.[16]

3.5. Cancer detection and individual risk assessment

Several early findings of clinical relevance have come from these trials that may assist individual risk assessment

protocols. Men with a 20% or greater reduction in their PSA values prior to biopsy after an initially elevated PSA had about half the risk of prostate cancer compared to the overall cohort (OR 0.43, 95% CI 0.35–0.52), with the greatest effect being observed in men aged 50–59 years.[17] No repeat PSA level confidently predicted the absence of prostate cancer. A raised PSA level in the presence of urinary symptoms indicated a reduced risk of prostate cancer (for example the odds ratio for nocturia four times/night: 0.44, 95% CI 0.22–0.83) whilst symptoms of sexual dysfunction were unrelated to disease risk in 8284 men.[18,19] An age-specific PSA reference range method for active monitoring of prostate cancer was compared to other methods using data from 408 ProtecT participants receiving active monitoring which revealed that the PSA velocity and doubling time methods became less sensitive over 3 years.[20]

A nested cohort study was conducted with nearly 1300 men aged 45–49 years and compared with men aged 50–69 years participating in the ProtecT study. Younger men attended the PSA recruitment clinics less frequently than older men (34%, 442/1299, compared with around 48% in the older men) but the detection rate of prostate cancer was comparable at 2.3% (10/442) with a PSA indication for biopsy of 1.5 ng/ml. In the younger men eight prostate cancer cases had at least two positive biopsy cores and three had perineural invasion. Nine cases were with Gleason score 6 (cT1c) and one was with a Gleason score 7 (cT2c).[21]

The ProtecT trial has facilitated investigation of the potential stage migration of prostate cancer that might arise from universal screening by utilising the low rate of opportunistic PSA testing in the UK. A sample of 2022 ProtecT participants with prostate cancer was compared with contemporaneous cases registered with the Eastern Cancer Registration and Information Centre (ECRIC).[22] The 3714 ECRIC cases had a higher age distribution, PSA levels, stage and grade of cancer (all comparisons $p < 0.001$) suggesting the potential stage migration if prostate cancer screening was introduced in the UK. The potential over-diagnosis of low risk disease was modelled to be around 20%.[23]

3.6. *Integrated research to understand trial conduct*

Qualitative research has explored ProtecT clinicians' and participants' perspectives revealing that the order and presentation of study information was crucial in making randomisation acceptable.[24] Concurrently, an RCT nested in the feasibility study identified that research nurses were equally effective and more cost-effective than urologists for randomisation appointments[25] so they were chosen for the main trial. More recently, different styles of information provision were shown to lead to variation in the knowledge of participants' about the trial and treatments.[26] A complex intervention was developed in the main trial for improving randomisation which comprised site visits, training, individual feedback and written guidance.[27]

4. Discussion

The CAP trial includes around 450,000 individuals from over 550 primary care centres which equates to about 8% of the male population of England and Wales aged 50–69 years. Over 110,000 men attended the ProtecT PSA clinics (although not all participated), and more than 1500 men with localised disease were randomised to the three treatments. Recent publications have given insights into the psychological impact of prostate cancer testing[12–14,16] and some clinical implications for improving the detection process.[17,18,21] Findings for both trials regarding prostate cancer-specific mortality will be published in around 2016.

The design and conduct of these trials have both strengths and some limitations. Cluster randomisation enhances the generalisability of CAP trial results through the universal geographical coverage whilst minimising volunteer bias and reducing contamination of the comparison group. PSA testing is infrequent in the UK,[28] although the incidence of disease has increased by 4% per annum in the 1990s, as in most other European countries.[29] The unbiased endpoint determination in both trials will ensure robust estimates of screening and treatment effectiveness. The rate of over-diagnosis of low risk disease in a screen-detected population will be established by comparison of incidence rates between the two CAP groups. High quality comparative effectiveness data will also be generated for active monitoring, surgery and radiotherapy treatments alongside extensive clinical and patient reported outcome data. Furthermore, the active monitoring cohort will allow the potential over-treatment of disease to be established through randomised comparison with radical intervention. Screening and treatment costs will be calculated, whilst lifetime costs, effects and cost-effectiveness can be modelled for different healthcare systems using probabilistic decision-analytic techniques (Dr. J. Wolstenholme, University of Oxford).

Limitations exist regarding the generalisability of trial results to non-white ethnic populations (less than 10% of ProtecT participants) and men younger than 50 years (only included in a pilot study). The single round of PSA testing in the CAP intervention group also does not reflect current screening practice in many countries. However, non-protocol PSA tests in the intervention group will be included in modelling of the impact of rescreening on the primary outcome. A strength of the ERSPC trial was the investigation of the screening interval; rescreening identified fewer aggressive cancers and that the optimal interval may be up to 8 years.[30] As in all intervention trials of long duration, the ProtecT trial evaluated the principal treatments used in the 2000s and so will be unable to account for implementation of any new technologies.

Findings on the impact of screening for prostate cancer from the UK trials complement the ERSPC results. Most men who participated in both studies were largely unaffected by the screening process, except for those predisposed to anxiety.[12,31] However, specific mood measures used in the ProtecT trial revealed more frequent (19% of men at biopsy) and persistent levels of distress (10% of men up to 3 months subsequently)[14] suggesting that previous measures may not have captured the full psychological effects of screening.[31] An active surveillance cohort linked to the ERSPC showed the feasibility of the treatment, although one quarter of the cohort received radical treatment within 15 months, possibly due to participant anxiety.[32] The long term outcomes of that cohort and the ProtecT active monitoring participants remain unknown.

There are two other comparative randomised trials for localised prostate cancer treatments, PIVOT and SPCG-4.[33]

Table 1 – Design characteristics of the CAP trial and ERSPC.

Trial characteristic	CAP trial	ERSPC
Randomisation unit	Primary care centre	Individual
Location	United Kingdom	7 European countries[a]
Eligibility criteria	Men aged 50–69 years	Men aged 55–69 years[a]
Recruitment period	2002–2008	1991–2003[a]
Recruitment total	>550 (ca. 450,000 individuals)	162,243 individuals[a]
Intervention group:		
PSA threshold (total PSA)	⩾3.0 ng/ml	⩾3.0 ng/ml (⩾4.0)[b]
DRE[c] with PSA testing	No	Yes[b]
Biopsy protocol	10 cores	6 cores[b]
Rescreening interval	Not in protocol	4 years (2–7)[b]
Treatment	Localised disease: randomisation or choice of active monitoring, radiotherapy or surgery Advanced disease: local policy	Local policy
Control group	Usual clinical care	Usual clinical care
Outcome ascertainment	Independent blinded adjudication committee	Independent blinded adjudication committee
Primary outcome	Prostate cancer-specific mortality	Prostate cancer-specific mortality
Follow-up	Average 10 years (up to 2016)	Median 9 years (up to 2007)[a]
Quality of life	Across intervention group	Several centres
Resource use	Across both groups	Several centres

[a] Core group for primary analysis.[1]
[b] Varied across centres and over time in core group.
[c] Digital rectal examination.

Surgery had disease-specific survival benefits in the SPCG-4 trial with early negative impacts on urinary symptoms and erectile dysfunction compared to watchful waiting in a largely incident cancer population.[34] These two interventions were compared in the PIVOT trial in a screen-detected population comprising one third African Americans with a primary outcome of overall mortality. The PIVOT trial has not yet reported results. The ProtecT trial will extend clinicians' and patients' knowledge regarding the impacts of active monitoring, radiotherapy and surgery on everyday life including symptoms, sexual function, quality of life, mood, anxiety and distress and the experience of living with the disease.

A comparison of the CAP and ERSPC trial designs reveals differences in the randomisation strategy, the eligibility criteria and cancer detection methods (summarised in Table 1). In addition, scheduled rescreening occurred in the ERSPC unlike in the CAP trial. The three main treatments for localised disease were allocated by randomisation or patient choice in the ProtecT trial whereas ERSPC treatment decisions were guided by local policies. Primary outcome measurement, including methods of ascertainment, is comparable in both trials. Neither trial has sufficient power to examine the effect of screening on all-cause mortality. There have been discussions regarding a possible meta-analyses, although this cannot be performed until 2016.

5. Conclusions

The CAP and ProtecT trials have already generated findings of clinical relevance which complement those of the ERSPC. The ProtecT trial will uniquely provide an evaluation of the comparative effectiveness of three major treatments for localised prostate cancer and the cluster design of the CAP trial will permit a robust estimate of the effect of a population-based screening policy. The CAP and ProtecT trials will report major outcomes in around 2016. Findings from these two trials will augment those of the ERSPC to enable worldwide health care providers to make decisions about the management of screen-detected prostate cancer and public health policy on screening.

Department of Health disclaimer

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Conflict of interest statement

None declared.

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