Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial

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Summary

Background **Prostate cancer is a major public health problem with considerable uncertainties about the effectiveness of population screening and treatment options. We report the study design, participant sociodemographic and clinical characteristics, and the initial results of the testing and diagnostic phase of the Prostate testing for cancer and Treatment (ProtecT) trial, which aims to investigate the effectiveness of treatments for localised prostate cancer.**

Methods **In this randomised phase 3 trial, men aged 50–69 years registered at 337 primary care centres in nine UK cities were invited to attend a specialist nurse appointment for a serum prostate-specific antigen (PSA) test. Prostate biopsies were offered to men with a PSA concentration of 3·0 μg/L or higher. Consenting participants with clinically localised prostate cancer were randomly assigned to active monitoring (surveillance strategy), radical prostatectomy, or three-dimensional conformal external-beam radiotherapy by a computer-generated allocation system. Randomisation was stratified by site (minimised for differences in participant age, PSA results, and Gleason score). The primary endpoint is prostate cancer mortality at a median 10-year follow-up, ascertained by an independent committee, which will be analysed by intention to treat in 2016. This trial is registered with ClinicalTrials.gov, number NCT02044172, and as an International Standard Randomised Controlled Trial, number ISRCTN20141297.**

Findings **Between Oct 1, 2001, and Jan 20, 2009, 228 966 men were invited to attend an appointment with a specialist nurse. Of the invited men, 100 444 (44%) attended their initial appointment and 82 429 (82%) of attenders had a PSA test. PSA concentration was below the biopsy threshold in 73 538 (89%) men. Of the 8566 men with a PSA concentration of 3·0–19·9 μg/L, 7414 (87%) underwent biopsies. 2896 men were diagnosed with prostate cancer (4% of tested men and 39% of those who had a biopsy), of whom 2417 (83%) had clinically localised disease (mostly T1c, Gleason score 6). With the addition of 247 pilot study participants recruited between 1999 and 2001, 2664 men were eligible for the treatment trial and 1643 (62%) agreed to be randomly assigned (545 to active monitoring, 545 to radiotherapy, and 553 to radical prostatectomy). Clinical and sociodemographic characteristics of randomly assigned participants were balanced across treatment groups.**

Interpretation **The ProtecT trial randomly assigned 1643 men with localised prostate cancer to active monitoring, radiotherapy, or surgery. Participant clinicopathological features are more consistent with contemporary patient characteristics than in previous prostate cancer treatment trials.**

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Introduction

Prostate cancer is the most frequently diagnosed cancer in men in developed countries, with an estimated 241 740 new cases and 28 171 deaths caused by the disease every year in the USA alone.[1] In the UK, it is the second most common cause of cancer deaths in men (13%) with 41 763 new cases diagnosed and 10 793 deaths caused by the disease in 2011.[2] The disease can be detected early by prostate-specific antigen (PSA) measurement followed by prostate biopsy. However, most screen-detected cancers are at low risk of progression, and potential harm could be caused by unnecessary diagnosis and treatment.

The publication of two population-based randomised controlled trials[3,4] of screening has not resolved this dilemma. The European Randomized Study of Screening for Prostate Cancer (ERSPC)[3] reported a clear but relatively small disease-specific survival benefit from screening compared with no active intervention at 8 years' and 13 years' follow-up, with a larger effect reported in a smaller Scandinavian cohort at 14 years after diagnosis.[4] By contrast, the US-based Prostate, Lung, Colorectal, and Ovarian (PLCO) trial[5] reported no benefit from screening with a similar length of follow-up, but was limited by substantial contamination from previous PSA testing in the control group in more than 50% of the unscreened men.

Most men diagnosed with PSA-detected prostate cancer tend to undergo radical treatment. Active monitoring or surveillance with deferred radical treatment has been

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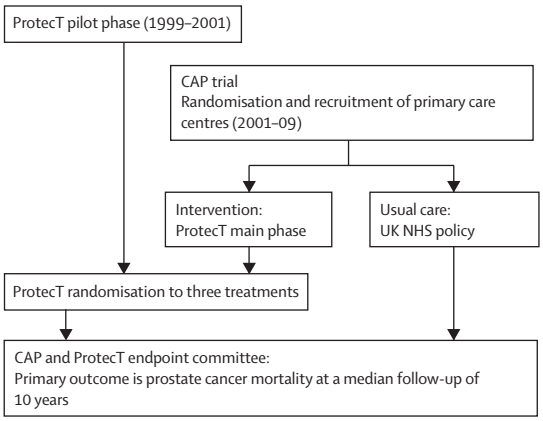

Figure 1: **ProtecT and CAP trial recruitment phases and endpoint assessment**
CAP=Cluster randomised triAl of PSA testing for Prostate cancer. ProtecT=Prostate testing for cancer and Treatment. NHS=National Health Service.

advocated to avoid immediate, potentially unnecessary, intervention. However, absence of evidence about optimal protocols precludes a clear definition of safety for this option. Two randomised trials[6,7] have compared radical surgery with passive observation (so-called watchful waiting). The US-based Prostate cancer Intervention Versus Observation Trial (PIVOT)[6] reported no overall mortality benefit from surgery in patients with PSA-detected cancer, whereas the Scandinavian Prostate Cancer Group 4 trial (SPCG-4)[7] showed a clear disease-specific and overall survival benefit for surgery in patients presenting clinically, as well as a reduction in progression to metastatic disease.

The Prostate testing for cancer and Treatment (ProtecT) randomised trial was designed to assess the effectiveness and cost-effectiveness of active monitoring (a surveillance protocol), external beam conformal radiotherapy with neoadjuvant androgen suppression, and radical prostatectomy for men with PSA-detected clinically localised prostate cancer. Analysis of the primary outcome of disease-specific mortality is scheduled for 2016, at 10 years' median follow-up. Here we present the trial design, the initial results of the PSA testing and diagnostic phase, and the clinical and sociodemographic characteristics of the randomly assigned participants.

Methods

Study design and participants

The ProtecT trial was designed in the late 1990s and early 2000s to compare the major conventional treatments for patients with clinically localised prostate cancer detected through population-based PSA testing. The three treatments were radical prostatectomy, external beam three-dimensional (3D) conformal radiotherapy, and active monitoring.

Recruitment was undertaken in two stages: a feasibility pilot in three English cities (in 24 primary care centres linked to three university hospitals) from June, 1999, to September, 2001 (ISRCTN08435261), and the main trial from October, 2001, to January, 2009, in nine cities (seven in England, one in Scotland, and one in Wales).[8]

Also in 2001, the CAP trial (Cluster randomised triAl of PSA testing for Prostate cancer; ISRCTN92187251) commenced, which is an extension to the ProtecT trial. The CAP trial randomly assigned primary care centres to undertake either the ProtecT trial or standard UK National Health Service (NHS) management (no routine PSA testing; figure 1), to assess population-based screening in addition to treatment effectiveness of clinically localised disease identified in ProtecT.[9] Further details of the CAP trial design and randomisation have been published previously.[10]

A written invitation was sent by 337 primary care centres assigned to undertake the ProtecT trial to registered men aged 50–69 years, excluding those with a previous malignancy (apart from skin cancer), renal transplant or on renal dialysis, major cardiovascular or respiratory comorbidities, bilateral hip replacement, or an estimated life expectancy of less 10 years. Men who responded received a ProtecT patient information sheet and an appointment with a specialist nurse who explained the complexities of PSA testing, assessed trial eligibility, and sought written informed consent. Previous PSA test results were checked in the medical records but were not an exclusion criterion. On postal receipt of a second written consent form, total PSA was analysed at site laboratories. Laboratories were audited by the NHS External Quality Assessment Service. Participants with a PSA concentration of at least 3·0 μg/L were invited to attend secondary care centres within the nine participating cities for a physical and digital rectal examination and standardised ten-core transrectal-ultrasound-guided prostate biopsies. Participants with an initial PSA concentration at least 20·0 μg/L at diagnosis were excluded because of the high likelihood that they had more advanced cancer.

Patients were staged using a combination of digital rectal examination, PSA concentration, transrectal ultrasound-guided biopsies, and isotope bone scanning (if PSA was ≥10 μg/L). MRI was used for staging at the discretion of individual investigators, because this imaging technique was not available in all centres during the recruitment period. Men diagnosed with clinically localised prostate cancer and deemed fit for radical treatment received a ProtecT treatment patient information sheet, and were subsequently invited to discuss randomisation with the specialist nurses. Men with a PSA concentration of 10 μg/L or higher or a Gleason score of greater than 7 points underwent an isotope bone scan to exclude metastatic disease. Men initially diagnosed with benign biopsy samples, or locally advanced or advanced prostate cancer, were managed within the NHS and excluded from the trial. Men with a benign first biopsy sample and a free-to-total PSA ratio below 11%, or atypical small acinar proliferation or

high-grade prostatic intraepithelial neoplasia, were offered further biopsies; if these repeat biopsy samples were benign, these men were managed in primary care and excluded from the trial. No further trial follow-up occurred after the one round of PSA testing or identification of cancers after referral to the NHS.

Approval was obtained from the UK Trent Multicentre Research Ethics Committee (01/4/025). Histopathologists at each site reported pathology findings on standardised forms and participated in trial quality control processes and those of the NHS Uropathology External Quality Assessment Scheme. The trial steering committee (seven independent members and chair) reviewed trial progress every year. Study training programmes and on-site monitoring visits were used to standardise trial conduct.[11,12]

Randomisation and masking

Men discussed treatment options with the specialist nurses, and if they agreed to the three-group randomisation (1:1:1), the nurse telephoned a central system in the Bristol trials' office (Bristol, UK) and logged participant details. Allocations were computer-generated as required for each participant, originally using Microsoft Excel functions, and subsequently in C++, stratified by site with stochastic minimisation to improve the balance across the groups in relation to age at primary care patient identification date, Gleason sum score (<7, 7, or 8–10 points) and mean of baseline and first biopsy PSA results (<6·0, 6·0–9·9, or >9·9 μg/L). The allocation was revealed after the entry of participant details, and then given to the participant by the nurse. Clinicians and participants were not masked to group assignment. Eligible participants were offered the choice of a two-group randomisation (radical prostatectomy or radiotherapy), or a three-group randomisation (with the addition of active monitoring to the two treatment groups). In 2003, the independent data monitoring committee (DMC) terminated the two-group option because of limited uptake, and the only option for participants who consented was the three-group randomisation throughout the remaining period of recruitment. Men who declined randomisation were offered identical follow-up and formed a comprehensive cohort within the study design.

Procedures

Participant sociodemographic characteristics, family history of cancer, and previous PSA tests were obtained at recruitment. Clinical management after diagnosis was standardised in the trial protocol using study group-specific pathways. In all treatment groups, androgen deprivation therapy was offered when serum PSA reached a concentration of 20 μg/L, or less if indicated. Imaging of the skeleton was recommended if serum PSA reached 10 μg/L, using isotope bone scintigraphy, plain radiographs, and MRI as necessary.

In patients randomly assigned to active monitoring, the protocol aim was to avoid immediate radical treatment while assessing the disease over time, with radical treatment offered if disease progression was evident. PSA concentrations were measured and reviewed every 3 months in the first year and twice yearly thereafter (frequency was changed as indicated). The specialist nurses also met with participants yearly to assess their overall health, and discuss graphical displays of PSA results and any concerns raised, overseen by each centre's local clinical investigator. Changes in PSA concentrations were assessed at each visit, and a rise of at least 50% during the previous 12 months triggered repeat testing within 6–9 weeks. If the PSA concentrations were persistently raised, or the patient had any other concerns, a review appointment was made with the centre urologist for discussion of further tests including re-biopsy and all relevant management options.

In patients randomly assigned to receive external beam 3D conformal radiotherapy, neoadjuvant androgen suppression was given for 3–6 months before and concomitantly with 3D-conformal radiotherapy delivered at 74 Gy in 37 fractions.[13] Quality assurance followed the RT01 trial procedures.[14,15] PSA concentrations were measured every 6 months for the first year and then yearly. The study oncologist held a review appointment with participants if the PSA concentrations rose by at least 2·0 μg/L post-nadir or concerns were raised about disease progression.[16] Management options were discussed, including continued monitoring, further tests, salvage, radical, or palliative treatments as indicated.

In patients randomly assigned to receive radical prostatectomy, the predominant approach was open retropubic radical prostatectomy with individual-level quality assurance according to minimum standards.[17] Participants with a baseline PSA concentration of at least 10 μg/L or a biopsy Gleason score of at least 7 points received bilateral lymphadenectomy. Postoperatively, PSA concentrations were measured every 3 months for the first year, every 6 months for 2 years, and then yearly. Adjuvant radiotherapy was discussed and offered to patients with positive surgical margins or extracapsular disease. The centre urologist held a review appointment with participants if their postoperative PSA concentrations reached 0·2 μg/L or higher to discuss adjuvant radiotherapy.

A linked translational study obtained biological specimens and epidemiological data.[9]

Outcomes

Outcome measures were selected for relevance to patients and health-care providers. The primary outcome was defined as definite or probable prostate cancer mortality, including intervention-related deaths, at a median of 10 years' follow-up. Participants were linked to the NHS national registry to obtain vital status information, with the information updated quarterly. The process used to assess cause of death was adapted from the PLCO algorithm[5] and ERSPC process[3] and then combined to

For the **study protocol** see http://www.nets.nihr.ac.uk/projects/hta/962099

assess deaths in both the CAP and ProtecT studies. The medical records of deceased participants were summarised by trained CAP researchers, anonymised, and reviewed by an independent endpoint committee who were masked to ProtecT and CAP trial[10] assignments (figure 1).

Secondary outcomes include overall mortality (taken from death certificates), and incidence of metastases, local disease progression, treatment complications, and resource use for the cost-effectiveness analysis (recorded on case report forms by specialist nurses every year from medical records and participant information). Patient-reported quality-of-life outcomes include the Expanded Prostate Index Composite (added in 2005 for rectal complications), International Consultation on Incontinence Questionnaire, International Continence Society (ICS) urinary ICSmaleSF and sexual function ICSsex measures, European Organisation for the Research and Treatment of Cancer QLQ-C30 (added in 2005 for cancer-specific effects), Hospital Anxiety and Depression Scale for psychosocial effects, and the Short Form-12 and EuroQol-5D generic health status measures.[18–25] These validated questionnaires were completed at recruitment, at first biopsy, 6 months after randomisation, and yearly thereafter for at least 10 years. Qualitative interviews investigated participants' experiences of treatments and outcomes. A full list of all prespecified outcomes can be found in our study protocol.

Statistical analysis

Before the start of the trial, a sample-size target of 1434 randomly assigned men (478 in each group) was identified as sufficient to estimate the absolute difference in mortality probability between two treatment groups with a 95% CI of ±0·045, on the basis of an assumed mortality rate of 15%, consistent with prostate cancer-specific mortality in men aged 55–69 years with clinically detected disease managed conservatively at that time and a difference that would be deemed clinically significant by the NHS. The pilot study recruitment data were used to calculate the number of sites and duration of recruitment needed to meet the sample size target. However, more recent data[10] suggested that disease-specific mortality with non-radical treatment was likely to be closer to 10% at 10 years, because of improvements in disease management. As a result, the DMC advised in 2008 that recruitment should continue to the planned end date, with 1590 men (530 per group) expected to be randomly allocated by that point. This sample size would enable a 46% reduction in prostate cancer mortality to be detected with 80% power at a 5% significance level for a pairwise comparison of a radical treatment with active monitoring. This calculation assumes a 10% prostate cancer-specific mortality at 10 years with active monitoring, and hence a 5·4% risk with radical treatment—an absolute difference very similar to the margin of error specified in the first calculation. These sample size targets are based on differences in and ratios of risk rather than the hazard ratios planned for the primary analysis, because the resulting calculations are simpler and more flexible. When a high survival rate is expected, calculations based on risk ratios will be a close approximation to those based on hazard ratios. The primary analyses will be done on an intention-to-treat basis comparing treatment groups as allocated. When a median of 10 years of follow-up has accumulated (November, 2015), the primary outcome measure of prostate cancer mortality will be compared between treatment groups using a survival analysis (Cox proportional hazards regression model) adjusted for stratification and minimisation variables. The estimated relative treatment effect for each pairwise comparison of treatments will be captured as a hazard ratio, and presented with a 95% CI. Hazard ratios are interpreted in the same way as rate ratios; the advantage of hazard ratios and Cox's proportional hazards model for this study is the accommodation of variation in the underlying rate of prostate cancer mortality during follow-up. Pairwise significance tests will only be done if a test of an equal 10-year disease-specific mortality risk across all three groups yields a p value of less than 0·05.[26] This approach will be used for event-based secondary outcomes—ie, grouped analyses of definite, probable, or possible prostate cancer, all-cause mortality, and metastatic disease.

Pairwise comparisons of symptom burden will use multilevel models for repeated measures to estimate the average treatment effect over the median 10-year follow-up. Further analyses will investigate the relative burden between treatment groups over time. Prespecified subgroup analyses will investigate whether treatment effectiveness in the reduction of prostate cancer-specific mortality is modified by baseline clinical stage, Gleason grade, age, or PSA concentration using stratified analyses for descriptive statistics and by formally including interaction terms in the relevant regression models. Secondary analyses will estimate the efficacy of radical treatment versus active monitoring in the reduction of prostate cancer mortality in individuals who complied with their allocated treatment, by using a method to derive an unbiased estimate in parallel with the per-protocol analysis originally specified in the trial protocol.[27,28] An analysis of primary and secondary outcome measures by trial group is reported yearly to the DMC. The DMC recommends changes to the trial steering committee if clear evidence (of the order of $p<0·001$) of a positive or negative balance of risks and benefits emerges for one intervention in comparison with the others.

Data from the recruitment, diagnostic, and randomisation phases are presented, and categorisation of continuous variables is either based on clinical thresholds (eg, for PSA) or the aim of equal group sizes (other measures). Resident area-based material and social deprivation scores (the proportion of people living in an

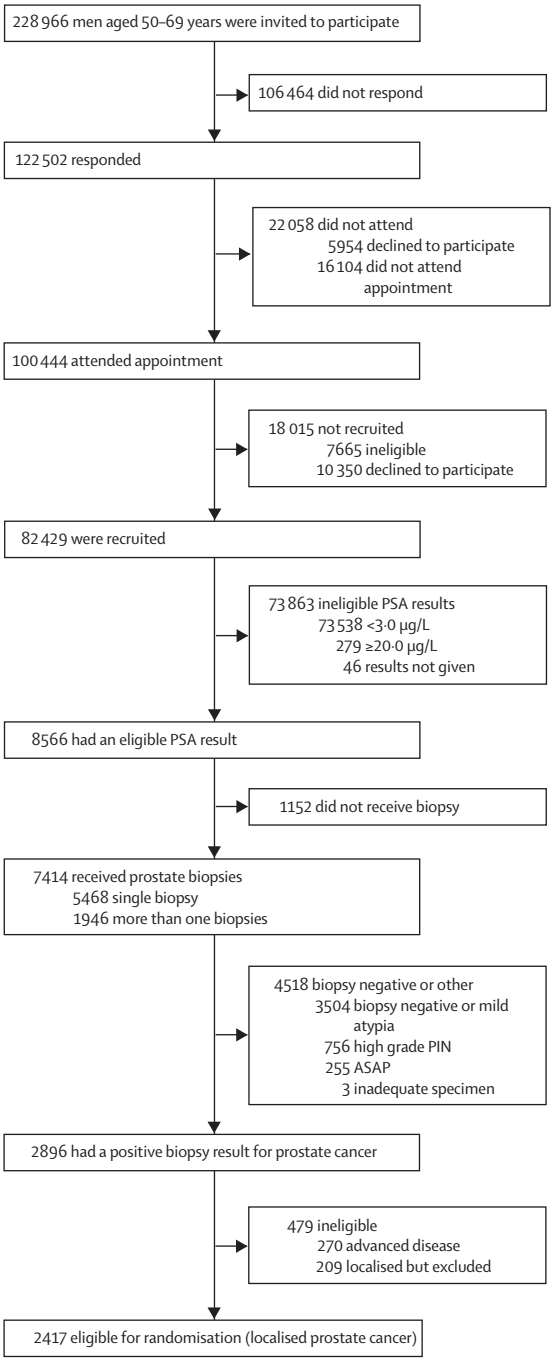

***Figure 2*: Flow diagram of the diagnostic phase of the main ProtecT trial**
Results are from one round of PSA testing. ASAP=atypical small acinar proliferation. PIN=prostatic intraepithelial neoplasia. PSA=prostate-specific antigen.

area of material deprivation) were derived using Lower Super Output Areas, each equating to around 1500 residents for England, Scotland, and Wales separately.

Analyses were done with STATA version 10. This study is registered as an International Standard Randomized Controlled Trial, number ISRCTN20141297, and with ClinicalTrials.gov, number NCT02044172.

	No prostate cancer diagnosed (n=79 208)*	Prostate cancer diagnosed (n=2896)	p value
Age (years)	58 (49–72)†	62 (49–70)†	<0·0001
Ethnic origin			0·10‡
White	77 486 (98%)	2839 (98%)	
African-Caribbean	215 (<1%)	11 (<1%)	
Other	1507 (2%)	46 (2%)	
Married or living with partner	66 178 (84%)	2420 (84%)	0·88
Living in area of deprivation§	10 706 (14%)	407 (14%)	0·34
Family history of prostate cancer	4082 (5%)	220 (8%)	<0·0001
PSA (µg/L)			<0·0001
Median (range)	0·9 (<0·1–19·9)	4·8 (3·0–19·9)	
Mean (SD)	1·3 (1·3)	6·0 (3·3)	

Data are median (range) or number (%), unless otherwise indicated. Results are from one round of PSA testing. PSA=prostate-specific antigen. *Ineligible participants were excluded (for 46 patients the PSA result was not available and 279 had a PSA concentration of ≥20 µg/L). †129 men were 49 years of age when the primary care list was generated, 120 of whom were 50 years old by recruitment; 25 men were 70 years or older at generation of the primary care list, of whom four were 71 years of age and one was 72 years of age; at the time of recruitment, all men who were enrolled fitted the stated inclusion criteria as per protocol. ‡p value is a result of the comparison between white ethnic origin and all other ethic origins. §Based on resident area-based material and social deprivation scores—eg, percentage of social housing.

***Table 1*: Demographic and clinical characteristics according to diagnosis of prostate cancer in patients recruited into the main ProtecT trial**

Role of the funding source

The funder had no role in the design or conduct of the study; in collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the report. JAL, FCH, JLD, and DEN had full access to all the data for this analysis (full outcome data will become accessible to them from Nov 15, 2015) and had final responsibility for the decision to submit for publication.

Results

Between Oct 1, 2001, and Jan 20, 2009, 228 966 men were invited to participate in the ProtecT study, of whom 122 502 (54%) responded, although 5954 (5%) of respondents declined to participate and 16 104 (13%) did not attend the appointment with the specialist nurse (figure 2). Of the 100 444 (44%) men who did attend, 82 429 (82%) were eligible and agreed to enrol. Of the men who attended their appointment, 10 350 (10%) did not enrol or return their second consent form and 7665 (8%) were deemed ineligible.

73 538 (89%) of the 82 429 recruited participants had a PSA concentration that was below the biopsy cutoff point. Only 279 (<1%) had PSA concentrations of 20 µg/L or higher and were referred for further assessment outside the trial. Of the men tested, 8566 (10%) were referred for biopsies, with high levels of uptake (7414 [87%]). The remainder (1152 [13%]) did not receive biopsies because they either opted to receive monitoring in primary care, or had comorbidities that precluded biopsies. Further

	Recruited (n=82 429)	Eligible for biopsy (n=8566)		Received biopsy (n=7414)		Diagnosed with prostate cancer (n=2896)		Proportion of tested patients with prostate cancer	
		n (%)	Unadjusted OR (95% CI)	n (%)	Adjusted OR† (95% CI)	n (%)	Adjusted OR† (95% CI)	Diagnosed/PSA tested (%)	Adjusted OR* (95% CI)
Age (years)†									
50–54	23 381 (28%)	1003 (4%)‡	NA	892 (89%)‡	NA	321 (36%)‡	NA	1·4%‡	NA
55–59	24 870 (30%)	2106 (8%)	2·06 (1·91–2·23)	1859 (88%)	0·91 (0·72–1·16)	693 (37%)	1·03 (0·87–1·22)	2·8%	1·01 (0·85–1·19)
60–64	19 859 (24%)	2766 (14%)	3·61 (3·35–3·89)	2397 (87%)	0·76 (0·61–0·96)	966 (40%)	1·10 (0·94–1·30)	4·9%	1·04 (0·89–1·22)
65–69	14 189 (17%)	2689 (19%)	5·22 (4·84–5·63)	2264 (84%)	0·62 (0·49–0·78)	915 (40%)	1·09 (0·92–1·28)	6·4%	0·98 (0·84–1·15)
PSA (μg/L)§									
<3·0¶	73 538 (89%)	0	NA	NA	NA	NA	NA	NA	NA
3–3·9	3689 (4%)	3689 (100%)	NA	3090 (84%)‡	NA	951 (31%)§	NA	25·8%‡	NA
4·0–9·9	4290 (5%)	4290 (100%)	NA	3785 (88%)	1·49 (1·31–1·69)	1568 (41%)	1·58 (1·43–1·75)	36·6%	1·66 (1·50–1·83)
10·0–19·9	587 (<1%)	587 (100%)	NA	539 (92%)	2·32 (1·70–3·17)	377 (70%)	5·15 (4·17–6·35)	64·2%	5·16 (4·25–6·26)

Percentages are calculated using previous category as a denominator. OR=odds ratio. PSA=prostate-specific antigen. NA=not applicable. *ORs for age were adjusted for PSA concentration, and ORs for PSA were adjusted for age. †Date of birth could not be obtained or age was out of eligible range for 130 recruited participants; age was out of eligible range for two participants invited for biopsy; two participants who received biopsy; and one participant who was diagnosed with prostate cancer. ‡Reference category. §PSA results were not available for 46 recruited participants, and 279 recruited participants had a PSA result of 20 μg/L or higher and hence were excluded. ¶Ineligible for biopsy.

Table 2: **PSA distribution, biopsy, and prostate cancer diagnosis by age and PSA concentration in the main ProtecT trial**

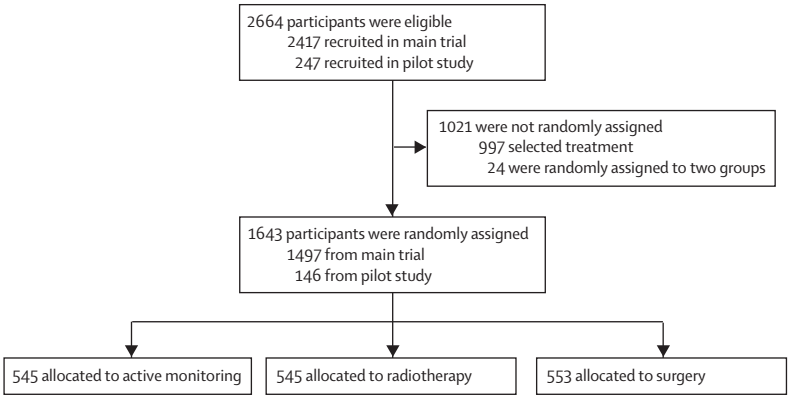

Figure 3: **Flow diagram of the randomisation phase of the ProtecT trial**

biopsies were offered to the 2357 (32%) men without a definitive diagnosis; 1563 (66%) of those offered underwent the repeat procedure, with a further 322 (14%) receiving a repeat biopsy after advice from a urologist.

2896 men were diagnosed with prostate cancer (4% of those recruited; 39% of those who had a biopsy). 2478 (86%) men with prostate cancer were diagnosed at initial biopsy with 418 (14%) diagnosed after repeat biopsies. 2417 (83%) of the men diagnosed with prostate cancer had clinically localised prostate cancer and were eligible for randomisation. Additionally, of men with a positive biopsy result, 270 (9%) were ineligible for randomisation because they had locally advanced, advanced, or metastatic disease, and 209 (7%) were excluded because of comorbidity.

Predominantly, recruited ProtecT participants were white and married or living with a partner, and 4082 (5%) reported a family history of prostate cancer (table 1). Median age was 58 years (range 50–69) in the total cohort, with slightly more men younger than 60 years recruited than older men (table 2), and 11 011 (13%) men had received a previous PSA test. A positive relation was noted between a raised PSA concentration, increased age, and receipt of biopsy. The proportions of patients who underwent biopsy were similar between all age groups (table 2). The relation between higher PSA concentrations and prostate cancer diagnosis was unchanged by adjustment for age, whereas the relation between the proportion of recruited patients diagnosed with prostate cancer and increased age was attenuated by adjustment for PSA concentration (unadjusted odds ratio [OR] data not shown; table 2). Ethnic origin, married or partnership status, and extent of material deprivation did not differ between participants diagnosed with cancer and those without cancer (table 1).

2417 men recruited to the main ProtecT trial were eligible, as were 247 from the feasibility pilot phase.[8] 1643 (62%) of these eligible patients agreed to randomisation (figure 3). The median age of all randomly assigned participants was 62 years (range 50–69) with a median PSA of 4·6 μg/L (range 3·0–19·9). Most participants with prostate cancer had T1c disease and a Gleason score of 6 points (table 3). The distributions of age, PSA results, Gleason scores, and disease stage were well balanced across randomised groups (table 3). The median follow-up is currently 8·6 years (IQR 7·1–10·4) and we have obtained vital status (primary outcome) info for 99% of patients, and secondary outcomes have been measured in 93%.

Of the 997 men who declined to be randomly assigned and expressed a preference for a particular treatment, 529 (53%) opted for active monitoring, 273 (27%) for radical prostatectomy, 133 (13%) for radiotherapy, 50 (5%) for brachytherapy, and 12 (1%) selected other treatments.

These participants had similar clinical and socio-demographic characteristics to those who were randomly assigned (table 4), except that they were less likely to reside in an area of material deprivation (OR of increased deprivation in randomised versus non-randomised participants of 0·74 [95% CI 0·58–0·94]).

Discussion

The ProtecT trial recruited and tested more than 82 000 community-based men aged 50–69 years. More than 8000 men had a PSA concentration of 3·0 µg/L or more, and of those, 87% received a biopsy, resulting in nearly 3000 men diagnosed with prostate cancer (4% of those recruited). Including eligible men recruited in the pilot study, 1643 (62%) of 2664 participants were randomly assigned to active monitoring, radical prostatectomy, or radiotherapy. In this initial report, median 8-year follow-up is more than 93% for all endpoints (99% for the primary outcome).

The ProtecT trial was designed to address key issues in the management of clinically localised prostate cancer, specifically the comparative effectiveness and cost-effectiveness of the three conventional treatment modalities, including the trade-off between early diagnosis with PSA testing and the risks of over-detection and over-treatment. Trial design features that will enhance the robustness of the findings include standardised diagnostic, treatment, and follow-up protocols; internal and external quality assurance processes; allocation concealment; high compliance with follow-up; extensive secondary outcomes; and an independent, masked primary endpoint committee. Randomisation was successful and baseline characteristics were evenly distributed across treatment groups. However, the study does have some limitations. The recruitment process was based on PSA testing, which is known to over-detect prostate cancer, and has the potential to be superseded by newer diagnostic modalities such as pre-biopsy imaging. Additionally, the long natural history of the disease means that the study will have taken more than 15 years to report, from first patient participation in 1999 to the planned analysis of primary outcome after a median 10-year follow-up in November, 2015. Furthermore, during the past decade radical surgery has evolved with the introduction of robot-assisted and laparoscopic techniques, but few of these new approaches were undertaken in this trial. Other treatments have also changed: brachytherapy, dose escalation, and intensity-modulated radiotherapy are not being assessed in ProtecT, and active surveillance cohorts now tend to focus on men with a Gleason score of 6 points and use scheduled prostate biopsies—eg, PRIAS (Prostate Cancer Research International Active Surveillance).[29] Another limitation is that the lack of ethnic diversity in the study population might limit the applicability of the ProtecT findings to non-white populations. Also, men younger than 50 years or older than 69 years were not eligible, nor

	Active monitoring (n=545)	Radiotherapy (n=545)	Radical prostatectomy (n=553)
Age at invitation (years)			
49–54	58 (11%)	62 (11%)	69 (12%)
55–59	140 (26%)	141 (26%)	137 (25%)
60–64	184 (34%)	176 (32%)	172 (31%)
65–69	163 (30%)	166 (30%)	175 (32%)
Median age (range)	62 (50–69)	62 (49–69)*	62 (50–69)
PSA (µg/L)			
3·0–5·9	373 (68%)	373 (68%)	371 (67%)
6·0–9·9	116 (21%)	121 (22%)	123 (22%)
≥10·0	56 (10%)	51 (9%)	59 (11%)
Median PSA (range; µg/L)	4·6 (3·0–20·9)†	4·6 (3·0–18·8)	4·7 (3·0–18·4)
Gleason score			
6	421 (77%)	423 (78%)	422 (76%)
7	111 (20%)	108 (20%)	120 (22%)
8–10	13 (2%)	14 (3%)	10 (2%)
Missing	0	0	1 (<1%)
Clinical stage			
T1c	410 (75%)	429 (79%)	410 (74%)
T2	135 (25%)	116 (21%)	143 (26%)

Data are number (%) or median (range). *One person was aged 49 years when the primary care list was generated, but fitted the stated inclusion criteria as per protocol. †One patient from the feasibility study had a serum PSA concentration of 20·9 µg/L at the specialist nurse visit; the concentration fell to 17·6 µg/L on repeat measurement and he became eligible for recruitment.

***Table 3*: Participant and clinical characteristics at randomisation in the ProtecT trial**

	Randomised (n=1643)	Non-randomised (n=997)	p value
Age (years)*	62 (49–69)†	62 (50–69)	0·60
Ethnic origin			0·31‡
White	1606 (98%)	984 (99%)	
African-Caribbean	10 (<1%)	2 (<1%)	
Other	37 (2%)	11 (1%)	
Married or living with partner	1375 (84%)	841 (84%)	0·72
Living in area of deprivation§	239 (15%)	111 (11%)	0·015
Family history of prostate cancer	119 (7%)	83 (8%)	0·28
PSA (µg/L)	5·8 (3·0)	5·8 (3·1)	0·67
Gleason score			0·42
6	1266 (77%)	755 (76%)	
7	339 (21%)	218 (22%)	
8–10	37 (2%)	24 (2%)	
Missing	1 (<1%)	0	
Clinical stage			0·96
T1c	1249 (76%)	758 (76%)	
T2	394 (24%)	239 (24%)	

Data are median (range) or number (%). *24 patients are classified as non-randomised because they were part of the early study with randomisation only between radical treatments (not active monitoring). †One person was aged 49 years when the primary care list was generated, but fitted the stated inclusion criteria as per protocol. ‡p value is a result of the comparison between white ethnic origin and all other ethic origins. §Based on resident area-based material and social deprivation scores using several indicators of income and living conditions—eg, percentage of social housing.

***Table 4*: Demographic and clinical characteristics at randomisation according to randomisation status in the ProtecT trial**

were men with a PSA concentration of 20 µg/L or higher because they were likely to harbour non-localised cancer and an increased risk of lymph node metastasis, as shown by Joniau and colleagues.[30] Although we acknowledge that recent advances in imaging techniques would have improved staging in these patients, only 279 (0·3%) of 82 429 participants in our tested cohort had a PSA concentration of 20 µg/L or higher.

Additionally, the recruited population could be generally healthier than the overall population, as often occurs in screening trials, but this does not affect the comparative effectiveness analyses of treatments.[3,5] Furthermore, UK statistics in 2008 suggested that prostate cancer mortality in the active monitoring group would be around 10% after 10 years—lower than expected at the trial outset. Therefore the mortality risk difference of 4·6%, upon which the original sample size was based, roughly corresponds to a hazard ratio of 0·54 in the revised calculation—a substantial benefit of radical compared with conservative management. Should results from this trial support early active intervention, evidence will be needed that benefits are sufficiently large to outweigh the well recognised complications of radical treatments.

The primary analysis will be highly informative for clinicians, patients, and decision makers because the trial has been designed to consider mortality, resource use, and quality-of-life outcomes. And, as with the other treatment trials, the findings will continue to be of interest as the data mature over time.

The study's limitations need to be balanced against a number of strengths that ensure that the ProtecT trial will be of pivotal importance in establishing the comparative effectiveness of the three most frequently used treatment options in PSA-detected clinically localised prostate cancer. It is the largest ongoing randomised controlled trial of prostate cancer treatments worldwide, with standardised protocols for diagnosis, treatment, and follow-up and enabling an assessment of screening through the linked CAP trial. The core age group of the ProtecT trial is similar to that of other randomised control trials. High levels of generalisability are assured by embedding ProtecT within the CAP randomised control trial of population-based PSA testing involving about 1·5% of all UK men aged 50–69 years recruited from randomly selected primary care centres. Participants with intermediate and some high-risk disease features were included and will help to establish whether active monitoring protocols can offer an alternative to immediate radical intervention in these patients. The planned subgroup analyses of treatment

	ERSPC (Europe)[3]	PLCO (USA)[5]	ProtecT (UK)	PIVOT (USA)[6]	SPCG-4 (Sweden)[7]
Interventions	Screening *vs* control	Screening *vs* control	AM *vs* RP *vs* RT	RP *vs* WW	RP *vs* WW
Recruitment period	1993–99	1993–2001	1999–2009	1994–2002	1989–99
PSA biopsy threshold (µg/L)	3·0/4·0	4·0	3·0	NA	NA
Number of biopsy cores	6	Variable	10	NA	NA
Men invited	68 896	NK	228 966	NA	NA
Men attended	NK	38 350	100 444	NA	NA
PSA tested (% of attendees)*	56 064 (29–91%)†	34 244 (89%)	82 559 (82%)‡	NA	NA
Raised PSA results	10%	8%	10%	NA	NA
Biopsy uptake	84%	32%	87%	NA	NA
Diagnosed with prostate cancer	2·7%	1·6%	3·5%	NA	NA
Randomly assigned to treatment	NA	NA	1643 (62%)	731 (15%)	695 (NK)
Age range, years (mean age)	55–69 (60–63§)	55–75 (60)	50–69 (61)	<75¶ (67)	<75¶ (65)
White ethnic origin	NK	86%	99%	62%	NK
Mean PSA, µg/L	NK	NK	5·8	10·1	13·0
Clinical stage*					
T1	42%	0·5%	76%	50%	11%
T2	28%	96%	24%	40%	75%
T3	11%	4%	0‖	0	0
Not recorded	17%	0·4%	0	10%	14%
Gleason score*					
2–6 (ERSPC 2–7)**	91%	63%	77%	74%	60%
7–10 (ERSPC 8–10)**	6%	31%	23%	19%	28%
Not recorded	3%	2%	0	7%	12%

AM=active monitoring. RP=radical prostatectomy. RT=radiotherapy. WW=watchful waiting. NA=not applicable. NK=not known. *Screening group. †Uptake varied across countries and methods of identifying men. ‡82% of attendees; 36% of all those invited. §Varied by country (ERSPC) or estimated from age distribution in quartiles. ¶Lower age limit unknown. ‖9% of patients had T3/advanced disease, but were ineligible for randomisation so are not shown here. **ERSPC Gleason grades 2–4 (15%) and 5–7 (76%) have been combined; 8–10 (6%).

***Table 5*: Design, and participant and clinical characteristics, of the principal screening and treatment trials in clinically localised prostate cancer**

Panel: Research in context

Systematic review

A systematic review of the evidence was done before the design of the trial and informed our protocol development. The review was commissioned by the Health Technology Assessment Programme of the National Institute for Health Research in the UK.[36] The following search terms were used for a text search within the title, abstract, and keywords: "prostate cancer" and related terms, and "therapy" (specifically "radiotherapy" and "prostatectomy"). The following databases were searched: Embase, CancerLit, Social Sciences Index, Sciences Index and PyscLit (1990–95), for articles published in all languages. No meta-analysis was possible because of the heterogeneity of extracted results. The systematic review concluded that there was insufficient evidence to establish the effectiveness or cost-effectiveness of screening or treatments for localised prostate cancer because of the shortage of robust randomised evidence at the time.

Interpretation

The ProtecT trial is, to our knowledge, the largest contemporary randomised controlled trial investigating the effectiveness of conventional treatment options in men with clinically localised prostate cancer detected after PSA testing. The ProtecT trial clearly differs from two previously published treatment trials[6,7] that compared surgery with watchful waiting (a passive observational option) in men with clinically detected disease (SPCG-4)[7] and older Veterans Administration men with PSA-detected disease (PIVOT).[6] In the ProtecT trial, these baseline results show that we successfully recruited men aged 50–69 years after community-based PSA testing and a high proportion agreed to be randomly assigned between the three major conventional contemporary options (surveillance, surgery, and radiotherapy), and have achieved high levels of follow-up. The data presented provide information about one round of testing and diagnosis in a population without extensive routine PSA testing. In 2016, the trial will publish its outcome data.

effectiveness by stage and grade will investigate this aspect and assist comparison with SPCG-4 and PIVOT treatment trial patients. Furthermore, the assessment of a radiotherapy and neoadjuvant regimen will be relevant for patients with higher risk disease because good evidence already exists for endocrine therapy combined with radiotherapy for advanced disease.[31]

ProtecT detected more prostate cancer in the first round of testing than did the ERSPC and PLCO trials, probably because of ProtecT's lower PSA threshold combined with the minimum ten-core biopsy protocol in a population previously unexposed to routine PSA testing. The clinical characteristics of the participants' cancers in the ProtecT trial are similar to those of other unscreened populations.[32] Cancer was generally detected at a lower stage and grade in ProtecT participants than in a UK cohort of patients with clinically detected prostate cancer in the early 2000s.[33] However, this reduction in stage and grade would have been mitigated by the upward grade migration reported in Gleason scoring in NHS practice between 2000 and 2010.[34] Nevertheless, the mean proportion of UK men whose PSA concentration has been tested remains low by international standards at 6% (range 2–9) in primary care centres in the mid-2000s. Compared with the PIVOT[6] and SPCG-4[7] treatment trials, ProtecT participants had the lowest PSA concentration, age, and included fewer higher stage cancers at the point of randomisation (table 5). Randomisation of eligible participants was higher in ProtecT (62%) than in PIVOT (15%), and other similar trials did not complete recruitment (eg, START, SPIRIT). The acceptability of randomisation in the ProtecT trial was enhanced by integrated qualitative research.[35] Most notably, ProtecT participants received active monitoring, not watchful waiting as in PIVOT[6] and SPCG-4.[7] Current active surveillance protocols have more restrictive entry criteria and rely more on scheduled re-biopsy than in ProtecT, but ProtecT trial results will provide, to our knowledge, the first randomised evidence for a monitoring strategy that includes the option of radical treatment (panel).

In 2016, the ProtecT trial will provide data for the comparative effectiveness and cost-effectiveness of active monitoring, radical prostatectomy, and radiotherapy in men diagnosed with localised prostate cancer after PSA testing with a median 10-year follow-up. These treatments are the major conventional options, and will be compared within an entirely PSA-tested cohort. The major findings will provide key information needed to underpin the management of clinically localised prostate cancer, including the crucial trade-off between survival gains and potential harm caused by over-detection and unnecessary radical treatment in PSA-detected prostate cancer.

Contributors

FCH, JLD, and DEN designed the ProtecT trial and obtained the funding. TJP and CM provided statistical expertise. JAL coordinated the trial, set up study procedures, and led follow-up assessment. FCH and DEN provided expertise in surgery, and MDM provided expertise in radiotherapy. MD, DD, LD, ELT, and EW were responsible for data management. JAL, FCH, JLD, and DEN had full access to the data used in this analysis and MD, EW, LD, and JAL had full access to some of the raw data. All authors contributed to the writing of the report, reviewing it for intellectual content, and have approved the submitted version. JAL, FCH, JLD, and DEN are the guarantors of the manuscript.

Declaration of interests

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