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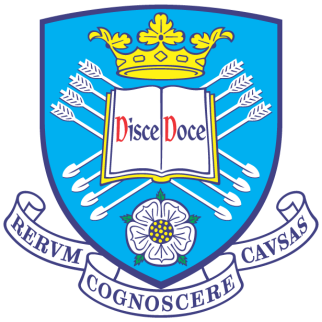

ScHARR

SCHOOL OF HEALTH AND RELATED RESEARCH

Option appraisal: screening for prostate cancer

Model update

Report to the UK National Screening Committee

March 2013

Version 1.0

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Executive summary

Aims and Objectives

The principal objective of the update to the ScHARR prostate cancer screening model is to incorporate the most recent data from the ERSPC screening trial. The original model was based on the results published in 2009, with median 9 years of follow up.[1] They reported a rate ratio of death from prostate cancer in the screened group of 0.80 (95% CI 0.65, 0.98), but no difference in all-cause mortality. In 2012 further results of the ERSPC trial were published with median 11 years follow up. The latest results show a rate ratio of death from prostate cancer in the screened group of 0.79 (95% CI 0.68, 0.91), but again no difference in all-cause mortality.[2]

Other key model parameters were also reviewed and updated where new evidence was available.
The mathematical model estimates the costs, benefits and resource implications of alternative screening options for prostate cancer in the UK. As in the original study the impacts of four screening options using the prostate specific antigen (PSA) blood test conducted are assessed in comparison to no screening and to each other:

- a single screen at age 50 years,
- screening every four years from age 50 to 74 years,
- screening every two years from age 50 to 74 years,
- screening every year from age 50 to 74 years.

Methods

The analysis comprises two components a model of prostate cancer natural history and screening and a screening impact model. The principal amendments to these component models are summarised below.
The natural history model was reprogrammed as a cohort model, the original version was implemented as a patient level simulation. The rebuilding as a cohort model was undertaken to allow more robust Bayesian calibration of the disease natural history model. This expanded calibration exercise exposed significant uncertainty in PSA sensitivity in the screening setting. The model was therefore calibrated to a range of different sensitivities and three scenarios are reported here relating to PSA sensitivities of 0.4, 0.6 and 0.8 for local prostate cancer. The model is calibrated to available UK and European data with the inclusion of the Schroder 2012[2] data on prostate cancer specific mortality.

There are three principal components to the impact model update:

- systematic searches for new evidence to inform key model parameters, and parameter revision where appropriate
- update costs to 2011/12
- explicit inclusion of treatment for sexual dysfunction in the model.

Literature searches included utility values, effectiveness of sexual dysfunction treatments, costs of prostate cancer treatments at end of life, adverse events associated with prostate cancer biopsy and treatment. The scope, databases searched and results (numbers of references identified) of each of the searches are shown in Appendix 2. Parameters were changed where there was new evidence. Notably a recent analysis from the ProtecT study reports adverse events and health care resource use of following prostate cancer biopsy.[3] 1.4% of men were admitted to hospital, most for sepsis, and 10.4% consulted a medical practitioner, most commonly their GP, primarily for infective or urinary symptoms. Previously data from the ERSPC was used, which gave a rate of post-biopsy hospitalisation of 0.47% (Raaijmakers 2002). The resource use, and hence costs, associated with biopsy-related complications have been revised in line with Rosario.[3]

Both the British Association of Urological Surgeons (BAUS) and the South West Public Health Observatory (SWPHO – for cancer registry data) were contacted for the latest treatment data by age group, cancer stage and Gleason grade. However the 2008 BAUS data, used in the original model, still appeared to be the most reliable and was used again, although Hospital Episode Statistics (HES) data (for radical prostatectomy numbers) and data from NatCanSAT (The National Cancer Services Analysis Team) on the total number of patients receiving radical and palliative radiotherapy treatment were used for calibration, as described in the main report. Costs were updated to 2011/12 using latest versions of the same cost sources, principally National Reference costs (2010/11)[4] and Unit costs of health and social care (2011).[5] Cost were inflated to 2011/12 values where necessary using the Hospital and Community Health Service (HCHS) inflation factors.[5]

The original model did not consider treatment for sexual dysfunction (SD). The study by Smith 2009 from which the prevalence of SD following treatment for PCa were derived reports long-term adverse event outcomes at 3 years, inclusive of treatment for adverse effects.[6] Furthermore they report an analysis showing that the use of a phosphodiesterase type 5 (PDE5) inhibitor appeared to have no effect on potency at 3 years.[6] For this reason no further adjustment was made for treatment

of SD. However, given that SD is the most common adverse effect of PCa treatment, there is evidence for the effectiveness of PDE5 inhibitors in some of this population,[7] and comments on the original model expressing concern as to the omission (R Firth, personal communication) the model was adapted to allow explicit consideration of treatment for SD. Data from the four PCa studies included in the Miles review[7] were extracted and meta-analysed to obtain an estimate of the proportion of men benefitting from treatment (see Appendix 5). The studies included patients who had bilateral or predominantly bilateral nerve sparing RP or radical RT. The overall treatment benefit (proportion of men with resolution of the problem) was 22.4% compared to placebo.

Results

Detection, stage distribution, survival and overall prostate cancer management duration.

A one off screen at age 50 years is estimated to have minimal impact on the long term incidence of PCa. However, more intensive policies can be effective in the early identification cancer, with four yearly and two yearly policies approximately doubling the lifetime risk of PCa from around 10% under no screening to around 20%. A small marginal increase in PCa identification is obtained by moving to an annual policy.

Overdetection has been defined as the detection of cancers in individuals who would otherwise have died of natural causes without a clinical diagnosis of PCa. All the repeat screening policies are estimated to entail approximately 45%-65% overdetection of PCa. Whilst the single screen policy has a lower rate of cancer detection, the overdetection rate is also reduced at around at30%-45%.

Potentially relevant cancers are defined as screen detected cancers that would otherwise arise clinically at a later date. The estimated mean lead time for potentially relevant cancers ranges from 8 to 18 years. This early detection is estimated to lead to a stage shift in cancers, with a fourfold reduction in metastatic cancers and more than doubling of local cancers.

The repeat screen policies are associated with an expected life years gained of approximately 0.05 to 0.12 years (20-67 days) for each individual invited for screening, with an equivalent figure of 0.01 (2-3 days) for the single screen policy. Whilst screening policies can often be associated with small expected gains for each individual, prostate cancer screening is also associated with an increased level of disease management, for instance for each life year gained the screening policies are associated with approximately 17-32 years of additional prostate cancer management.

The single screen at 50 policy is estimated to have a minimal impact on overall prostate cancer incidence and mortality rates, being the least effective policy in terms of relative rate of prostate

cancer mortality. However, this policy also entails the least expected excess prostate management to obtain one additional life year gained.

Treatment

The analysis shows that screening once at age 50 (policy 1) has little effect on current treatment patterns apart from a small rise in radical treatment following the screen. Radical treatment in the screened age groups increases with screening intensity. The more frequent the screening (policies 1 through to 4), the more radical treatment in the screened age groups. Assuming treatment patterns remain constant, radical treatment would increase up to 3 times for repeat screening policies, primarily in men aged less than 75 years.

Adverse effects of diagnosis and treatment

Serious adverse effects of biopsy are infrequent, but nevertheless a proportion of men (1.4%) are hospitalized for infection resulting from biopsy.[32] This will result in an additional 4500 men being affected for a four yearly screening policy.

The incidence of long term adverse effects of treatment increases with screening intensity. By far the most common adverse effect of treatment for prostate cancer is sexual dysfunction. Regular screening with a frequency of one to four years would increase the number of men affected by between 19,000 and 25,000, depending on policy. Screening policy also affects the age at which adverse events occur. If men are treated at a younger age for PCa as a result of screening they will also incur adverse effects earlier, and have to live with them longer

QALYs (Quality adjusted life years)

QALYs allow differences in quality of life to be taken into consideration as well as differences in survival. The net incremental QALYs reflect potential increases in overall survival resulting from screening (although the ERSPC found no statistically significant increase)[2] as well as the negative effects of harms of treatment. All screening policies result in loss of discounted QALYs: for repeat screening the loss ranges from 0.016 to 0.023 per man invited for screening. A sensitivity analysis with a discount rate for benefits of 1.5% (baseline 3.5%) also shows a loss in discounted QALYs with screening. The loss in QALYs reflects the adverse effects of treatment. Univariate sensitivity analysis showed that discounted QALYs remained negative for all of the screening policies when varying model parameters.

Resources

Routine screening for prostate cancer clearly will have a significant impact on resource use, both for screening and diagnosis of cancers, but also for the treatment or monitoring of cancers that would otherwise remain unidentified. The resources most impacted are those required for screening itself. Policy 4 (annual screening) would result in almost 10 million more PSA tests per year and 1.4 million biopsies. Whilst a large increase in many resources would be required (e.g. GP nurse sessions, PSA tests, radical treatments, hormone treatment, outpatient appointments) there would be some small savings in others relating to the diagnosis and treatment of more advanced disease such as MRI scans, treatment for hormone-refractory cancers and terminal care.

Costs

The total additional lifetime discounted costs for a cohort of men aged 50 of a screen once policy at 50 are £58 million, rising to over £1 billion for an annual screening policy. Note costs are discounted to age 50 for all policies and **do not include the costs of administering a screening programme.** The ratio of screening to treatment costs rises with more frequent screening as the ratio of cancers detected to the number of men screened falls. With an annual screening policy the costs of screening are greater than those for treatment.

Conclusions

This update was undertaken primarily to assess the implications of longer term mortality results being published from the ERSPC trial and the opportunity was taken to revise the model structure and implementation. The reprogramming and recalibration of the model exposed significant uncertainty in the sensitivity of the PSA test in the screening setting, explored with a scenario analysis. The longer term mortality results published in 2012 were modestly improved compared to those released in 2009 and in line with this the results in this update are modestly improved particularly in the scenario assuming a low PSA sensitivity of 0.4 for local disease.

A single screen at age 50 has little long term impact on overall age specific prostate cancer incidence and mortality rates. Intensive annual screening has little marginal benefit over a policy of screening every two years. Screening policies every two and four years are estimated to impact on early diagnosis and stage at diagnosis of prostate cancer. Cancers that would have been clinically diagnosed with background PSA testing at the level that was prevalent in 2004, would be diagnosed on average 8-16 years earlier. The two and four year screening policies are associated with overdetection rates of between 36% and 54%.

In order to obtain 1 additional year of life the modelling suggests that the repeat screening policies are associated with in the region of 22-32 years of additional prostate cancer management, with an equivalent figure of 17-30 years for the single screen at age 50 years policy. The results are consistently most positive for the scenario assuming a low PSA screening sensitivity.
Despite the impact on stage at diagnosis trials do not demonstrate any overall survival benefit from screening, this modelling suggests that overall expected survival benefit is likely to be small, in the region of 2-4 days per person invited for screening for the single screen at 50 policy and 20-60 days for the repeat screen policies.

Assuming treatment patterns remain constant radical treatment would increase by radical treatment would increase up to 3 times for a repeat screening policy, primarily in men aged less than 75 years. The incidence of long term adverse effects of treatment (urinary symptoms, bowel function, sexual dysfunction) would rise accordingly, and shifts the incidence to younger age groups, hence increasing prevalence.

Despite predicting marginally improved survival for PCa screening policies the model shows discounted QALYs are negative for all screening policies, a result that is consistent across different scenarios and sensitivity analyses. Thus the harms of adverse effects of treatment outweigh the potential survival benefits.

Routine screening for prostate cancer clearly will have a significant impact on resource use, both for screening and diagnosis of cancers, but also for the treatment or monitoring of cancers that would otherwise remain unidentified. The resources most impacted are those required for screening itself. Policy 4 (annual screening) would result in almost 10 million more PSA tests per year and 1.4 million biopsies. Whilst a large increase in many resources would be required (e.g. GP nurse sessions, PSA tests, radical treatments, outpatient appointments) there would be some small savings in others relating to the diagnosis and treatment of more advanced disease.

The total additional discounted costs of a screen once policy at 50 are £58 million, rising to over £1 billion for an annual screening policy. Note costs are discounted to age 50 for all policies and **do not include the costs of administering a screening programme.** The ratio of screening to treatment costs rises with more frequent screening as the ratio of cancers detected to the number of men

screened falls. With an annual screening policy (4) the costs of screening are greater than those for treatment.

Contents

Abbreviations

AM	active monitoring
3DCRT	3-dimensional conformal radiotherapy
BAUS	British Association of Urological Surgeons
BPH	benign prostate hyperplasia
CEA	cost-effectiveness analysis
DRE	digital rectal examination
ERSPC	European Randomised Study of Screening for Prostate Cancer
HT	hormone therapy
LHRHa	luteinizing-hormone-releasing hormone analogue
MRI	magnetic resonance imaging
NI	Northern Ireland
NICE	National Institute for Clinical Excellence
NSC	National Screening Committee
OCM	other cause mortality
ONS	Office for National Statistics
PCa	prostate cancer
PCOS	Prostate Cancer Outcome Study
PIVOT	Prostate cancer Intervention Versus Observation Trial
PLCO	Prostate, Lung, Colon, Ovary trial
ProtecT	Prostate testing for cancer and Treatment
PSA	prostate specific antigen
QALE	quality-adjusted life expectancy
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RP	radical prostatectomy
RT	radiotherapy
SD	sexual dysfunction
SWPHO	South West Public Health Observatory
TNM	Tumour, Node, Metastasis staging of tumours: T – primary tumour; N – regional nodes; M – metastases
TRUS	transrectal ultrasound
TURP	transurethral resection of the prostates
WW	watchful waiting

1.0 Aims and Objectives

The principal objective of the update to the ScHARR prostate cancer screening model is to incorporate the most recent data from the ERSPC screening trial. The original model was based on the results published in 2009, with median 9 years of follow up.[1] They reported a rate ratio of death from prostate cancer in the screened group of 0.80 (95% CI 0.65, 0.98), but no difference in all-cause mortality. In 2012 further results of the ERSPC trial were published with median 11 years follow up. The latest results show a rate ratio of death from prostate cancer in the screened group of 0.79 (95% CI 0.68, 0.91), but again no difference in all-cause mortality.[2]

Other key model parameters were also reviewed and updated where new evidence was available.

The mathematical model estimates the costs, benefits and resource implications of alternative screening options for prostate cancer in the UK. As in the original study the impacts of four screening options using the prostate specific antigen (PSA) blood test conducted are assessed in comparison to no screening and to each other:

- a single screen at age 50 years,
- screening every four years from age 50 to 74 years,
- screening every two years from age 50 to 74 years,
- screening every year from age 50 to 74 years.

2.0 Methods

Model Overview

The analysis presented here comprises a natural history and screening model and a separate screening impact model. This structure is similar to the original assessment and detailed descriptions for the two components based closely on the original report are reproduced in Appendix 1. The work undertaken to update the model is summarised in the following sections.

2.1 The natural history and screening model

A cohort simulation model of prostate cancer screening is built that allows the impact of different screening policies on cancer diagnosis and subsequent survival to be assessed. The model comprises prostate cancer natural history and epidemiology components together with a model of screening management. The model used in the original assessment was designed and built as a patient level simulation, the rebuilding as a cohort model was undertaken to allow more robust Bayesian calibration of the disease natural history model. The cohort model for this update uses the same conceptual disease model as the original model and likewise is calibrated to available UK and European data regarding prostate cancer incidence and screening with the modification that a) the update uses the Schroder 2012[2] data on prostate cancer specific mortality b) the exclusion of the Roemeling 2006[8] data and c) the new model uses the BAUS Registry data for calibration rather than validation as in the original model.

The natural history and screening model is implemented in Excel. It estimates the number of cancers detected, their severity and progression through the underlying disease states of local, locally advanced and metastatic cancers for different screening scenarios. The screening impact model estimates the impact of different screening policies on incremental resource use, costs, and harms to men from the adverse effects of treatment.

As described above the reprogramming of the prostate cancer screening model as a cohort model instead of a patient level model was to enable more robust calibration of the natural history and test characteristics parameters. The use of a cohort model allows a) longer calibration runs to be used to ensure convergence in each run and b) more repeated calibration runs to ensure that the model converges to global rather than local minimum parameter sets. This allows improved evaluation of the robustness of the model, in particular this exposed a high degree of uncertainty in the sensitivity

of the PSA test in the screening context (and related natural history) to the degree that the model fails to converge reliably to a single global solution. Whilst there was some suggestion that the model was highly sensitive to PSA sensitivity in the original modelling exercise and a discussion to this effect is included in the original report, the use of the patient level model meant that this uncertainty could not be explored fully due to model runtime constraints. In order to analyse the impact of this uncertainty the cohort model was calibrated to a range of PSA test sensitivities and three scenarios are presented here relating to sensitivities of 0.4, 0.6 and 0.8, with baseline results presented for a PSA sensitivity of 0.6. Parameter sets and model predictions derived from the calibration exercise are presented in Appendix 1.

2.2 The screening impact model

There are three principal components to the impact model update:

- Systematic searches for new evidence to inform key model parameters, and parameter revision where appropriate
- Update costs to 2011/12
- Explicit inclusion of treatment for sexual dysfunction in the model.

All the parameters used in the screening impact model are shown in Appendix 3

2.2.1 Literature Searches

Searches were undertaken August/September 2012 for literature to inform model parameters. They included searches for the following parameters:

1) Utility values for prostate cancer
2) Prevalence of sexual dysfunction in general population by age
3) Effectiveness of sexual dysfunction treatments
4) Cost effectiveness of treatments of prostate cancer at end of life/mHRPC
5) Adverse events associated with prostate cancer biopsy
6) Adverse events associated with prostate cancer treatments

The scope, databases searched and results (numbers of references identified) of each of the searches are shown in Appendix 2. The literature identified to review the model parameters is discussed below.

In addition a search on Medline was conducted (August 2012, updated January 2013) to identify if there were any recent publications from the UK ProtecT (Prostate Testing for Cancer and Treatment) study which were relevant. One study was identified, that by Rosario et al.[3] on PCa biopsy, also identified in search (5).

2.2.2 Model Parameters

Estimation of resources required to diagnose cancers detected by a screening programme

These parameters remain unchanged (ratios PSA tests/positive PSA tests by age, cancers detected/PSA tests by age, refuse biopsy by age).

Treatment of localised and locally advanced cancers

Both the British Association of Urological Surgeons (BAUS) and the South West Public Health Observatory (SWPHO – for cancer registry data) were contacted for the latest treatment data by age group, cancer stage and Gleason grade. (In the original model BAUS 2008 data was used (personal communication Sarah Fowler, February 2010). BAUS stopped collecting this type of data March 2011, and returns fell in the preceding years (2008 (used in last analysis) 14,700 returns, 2009 13,000 returns, 2010 9,300 returns (personal communication Sarah Fowler, March 2012). The number of returns for localised cancers with Gleason grade data is 10% lower in 2009 compared to 2008, and RT appears to have be very low compared to the previous year (from 16.5% to 5.6%), suggesting it is very poorly reported in the later year unless there was a large shift in treatment away from RT. The BAUS 2008 data, although older, therefore appears to be a more reliable source of data than that for the later years.

The latest available cancer registry data (2009) shows the incidence of prostate cancer to be 34,793 in England. Of these 93% were of unknown stage. Of cancers with known stage there were only 1300 localised cancers with known treatment (of a total of approximately 23,000 localised cancers). (Personal communication Luke Hounsome, October 2010.)

There are other sources which capture total treatment numbers for prostate cancer, but without the level of detail required regarding the patient age and cancer Gleason grade. Hospital Episode Statistics (HES) 2011/12 report a total of 5572 radical prostatectomies (OPCS code M61) in England of which 1549, 3891 and 132 for men aged <60 years, 60 – 74 and 75+ years respectively.[9]The RTDS (National Radiotherapy Dataset) annual report 2010/11 reports that 35.1% of the number of incident PCa cases had radical radiotherapy in England.[10] Applying that proportion to the total

number of incident PCa cases of 34,892 (ONS 2010)[11] means there were 12,247 patients treated with radical RT in England. It also reports 24.7% of the number of incident cases were treated with palliative RT, or 8,618 patients in England. Assuming treatment is similar across the UK the data suggests a total of 6,540 PCa patients are treated with RP annually, and 14,380 with radical RT.

These summary numbers were used to adjust the baseline 2008 BAUS data as follows.

- The total number of RP in England was assumed to be as reported in HES 2011/12 data (5572). The shortfall was made up with members of the other/unknown category. The allocation took into account that some patients (10%) initiated on AM would later have radical treatment (RP or RT alone). The distribution of RP across the age/Gleason groups was done using proportions calculated from the BAUS 2008 data. An exception was the allocation to those aged over 80, which was set to zero.

- The total number of radical RT treatment is 12,247 (see above) and these include treatments for locally advanced as well as localised cancers. Attributing the remainder of the other/unknown category with localised and locally advanced cancers to RT gave a total of RT treatments of 12,592. The distribution of RP across the age/gleason groups was done using proportions calculated from the BAUS 2008 data.

- Note this allocation is somewhat arbitrary, and in particular the distribution of RT across localised and LA cancers is unknown. However it does have the advantage that the number of radical treatments in the baseline model approximate to the best available data on the total numbers of RT and RP.

- The distribution of each of these treatments by age/Gleason grade was assumed to be as the BAUS 2008 data.

The allocation process resulted in the distribution of treatments for each age/Gleason grade patient group with localised and locally advanced cancers shown in Tables 1 and 2.

Table 1 Treatment allocation used in the model for localised prostate cancer

Age	Gleason score	RP	RT	HT	RT + HT	AM / WW
< 70	<7	37.9%	19.6%	2.6%	10.9%	29.1%
	7	41.3%	10.5%	10.2%	32.2%	5.7%
	>7	25.7%	5.0%	28.6%	38.3%	2.4%
70-79	<7	13.3%	10.6%	9.7%	22.0%	44.3%
	7	10.5%	10.3%	20.9%	44.4%	13.8%
	>7	7.8%	3.1%	44.1%	41.8%	3.2%
>= 80	<7	0.0%	0.0%	23.4%	3.4%	73.2%
	7	0.0%	0.0%	58.6%	4.7%	36.7%
	>7	0.0%	0.0%	87.1%	1.8%	11.1%
Total	<7	27.9%	15.6%	6.0%	14.1%	36.4%
	7	25.8%	9.8%	17.9%	35.4%	11.1%
	>7	13.1%	3.3%	44.7%	34.9%	4.0%
	Total	24.8%	11.4%	16.6%	25.6%	21.6%

Table 2 Treatment allocation used in the model for locally advanced prostate cancer

Age	HT	RT + HT
< 70	43.9%	56.1%
70-79	50.9%	49.1%
>= 80	93.7%	6.3%
All	57.3%	42.7%

The resource use assumed for the treatment and monitoring of localised cancers remain unchanged. The management of patients on AM is particularly uncertain. The 2011 review of the prostate cancer clinical guideline CG58 looked at evidence for the content of AM, and found no studies comparing different active surveillance strategies.[12] The guideline on AM remains unchanged, as do the model assumptions re resource use for AM.

Treatment of men with LA cancers

Recent evidence indicates that PCa mortality is reduced if men with LA or high risk localised cancers are treated with RT in addition to HT, albeit at the cost of increased adverse effects of treatment (see CG58 review 2011, study by Widmark et al 2009).[12] This evidence may change future recommendations, and lead to an increase in RT treatment for these patients, with both additional costs and benefits.

Treatment of hormone refractory PCa

The literature search identified no new studies on total treatment costs for patients with metastatic hormone-resistant PCa. The original model used Collins (2005),[13] which assumes initial cytotoxic therapy with docetaxel, and subsequent care including additional chemotherapy and hospitalisation for palliative care. Docetaxel is still considered the first line treatment of choice for patients suitable for cytotoxic therapy. New drugs have emerged for further treatment, Cabazitaxel and Abiraterone. The former was rejected for use rejected for use by NICE.[14]

Arbiterone was accepted by NICE for second line treatment following docetaxel, but only with a discount on drug costs, the degree of discount being confidential.[15] This is therefore likely to increase costs for these patients. The other change is that docetaxel is now generic, but due to differing vial sizes and concentrations it is difficult to compare the prices used by Collins with those current. Thus some treatment costs are likely to have risen and others fallen, but it is not possible to quantify these changes. The (inflated) costs of care for this patient group from Collins have been used, as in the original model.

Adverse Effects of diagnostic tests, biopsy and treatments for PCa

Recently there have been some reports from retrospective analyses of records that infection rates have increased following prostate biopsy due to antibiotic resistance (Nam 2010,[16] Loeb 2010[17]) but another did not find the same effect (Dodds 2011)[18], albeit over a shorter timescale (7 years compared to 9 years (Nam) and 16 years (Loeb)). Two recent UK studies report similar rates to each other for hospitalisations following prostate cancer biopsy. Ganeshwaran (2011) undertook a retrospective analysis of 600 men undergoing the procedure between 2007 and 2010 in Scotland.[19] The 30 day hospitalisation rate for urological complications for men without cancer was 1.3%. A prospective analysis nested within the ProtecT study reports adverse events and health care resource use of following prostate cancer biopsy in 1144 asymptomatic men who were invited for a PSA test between 1999 and 2008 (Rosario 2012).[3] 1.4% (95% CI 0.8%, 2.4%) of men were admitted to

hospital, most for sepsis. A further 10.4% (8.7%,12.3%) consulted a medical practitioner, most commonly their GP, primarily for infective or urinary symptoms. The resource use (and hence costs) associated with biopsy related complications have been revised in line with Rosario.[3]

Given the increased rate of hospital admissions post-biopsy consideration was given to loss of quality of life resulting from this. A search of medline for sepsis AND (eq5d OR eq-5d OR euroqol OR qwb OR hui2 OR hui3 OR 15d OR sf-6d OR sf6d OR aqol) identified 22 papers. Of these only one reported a utility for sepsis, and this was in the context of pneumonococcal disease (Galante 2011).[20] The study used vignettes to describe health states, but these were not reported, so the severity of the state is not clear. In the UK the EQ-5D utility was -0.295 (95% CI -0.359, 0.231). Given the severity for sepsis post-biopsy may be less than that in pneumonococcal disease a baseline value of 0 for utility was used, with the sensitivity of the model to the value tested in sensitivity analysis using the 95% confidence intervals from Galante.[20] The duration of a hospital admission was taken from National Reference cost data, a value of 4.7 days.[4]

It is also of note that a significant minority of men in the Rosario study reported moderate to severe pain following the procedure (7. 3%), and 19.6% of men reported a negative attitude to a repeat biopsy.[3] Loeb (2012) in an analysis of the Rotterdam ESRPC data also found an increased risk of adverse effects of repeat biopsy compared to first biopsy including haematuria (OR 1.4) and pain (OR 1.6).[17] Note no disutility has been associated with PCa biopsy itself in the model.

Adverse effects of treatments for localised PCa

A literature search was undertaken to identify if there were any significant new studies to inform the prevalence of post-treatment harms used in the model. It identified a comprehensive systematic review of the benefits and harms of treatments for localised PCa undertaken by the U.S. Preventive Services Task Force (Chou 2011).[21] The review was used to identify if there was any significant new data which required the parameter values used in the model to be revised. Apart from the addition of a sensitivity analysis on the prevalence of urinary symptoms following RP (+22% compared to AM, baseline +14%) no changes were made. More details of the review of the model parameters used for adverse events of treatment in comparison with the Chou review and meta-analysis are reported in Appendix 4.

Utility

The updated search identified no further studies reporting utilities of adverse event states associated with treatment for PCa derived using the EQ-5D or other measure using patient described states valued by the general public, as required by NICE (NICE Guide to the methods of technology appraisal June 2008[22]).

For comparison the results of a review of PCa utilities derived using all standard methods are shown below in Table3*.[23] Those used in the model are sexual dysfunction 0.9, urinary function 0.94 and bowel function 0.89.

Table 3 Utility values derived using all standard methods (Bremner 2007)[23]

	Sexual dysfunction		**Urinary function**		**Bowel function**	
	N studies	**Mean utility**	**N studies**	**Mean utility**	**N studies**	**Mean utility**
Mild/moderate	4	0.95	11	0.93	8	0.80
Severe	21	0.85	12	0.72	2	0.91*

*As reported by Bremner, utility higher for more severe bowel problems, but note small number of studies

Unit costs

Unit costs were updated to 2011/12 using latest versions of the same sources, principally National Reference costs (2010/11)[4] and Unit costs of health and social care (2011).[5] Cost were inflated to 2011/12 values where necessary using the Hospital and Community Health Service (HCHS) inflation factors.[5] Exceptions are listed below. All unit costs and their sources are shown in Appendix 3.

Hormone treatment

Prescription Cost Analysis data 2011 shows that the most commonly prescribed hormone therapy for PCa remains goserelin in the form of Zoladex LA 10.8mg. This costs £235 for a dose lasting 12 weeks (BNF 2012).[24]

Prostate cancer biopsy

This was originally costed from the HRG national tariff cost for needle biopsy of the prostate (£266* market inflation factor 1.12 = £298 in 2008/9). However the procedure is no longer listed in the national tariff data. The OPCS code is M452 (diagnostic endoscopic examination of bladder and

biopsy of lesion of prostate), which maps to HRG code LB15 (Bladder Minor Procedure). The national average adult day case cost (£350) for this HRG group has been used as the cost of prostate biopsy (National reference costs 2010/11).[4]

Treatment for sexual dysfunction

The original model did not consider treatment for sexual dysfunction. The study by Smith 2009 from which the prevalence of SD following treatment for PCa were derived reports long-term adverse event outcomes at 3 years, inclusive of treatment for adverse effects.[6] Furthermore they used their data to analyse the effect of treatment on potency. They report:

"At three years 494 men (33% of cases) reported that they had used some form of treatment to achieve an erection.…Of the men who reported seeking assistance for erectile function 383 (77.5%) stated that they used a phosphodiesterase type 5 inhibitor (for example sildenafil, tadalafil, or vardenafil (Viagra, Cialis and Levitra, respectively)), although 168 (43.9%) of these individuals stated that such agents were of "little or no use". After adjusting for age, baseline potency, and treatment type, use of a phosphodiesterase type 5 inhibitor appeared to have no effect on potency at 3 years."[6] For this reason no further adjustment was made for treatment of adverse effects. However, given that SD is the most common adverse effect of PCa treatment, there is evidence for the effectiveness of PDE5 inhibitors in this population (Miles 2012), and comments on the original model expressed concern as to the omission (R Firth, personal communication) the model was adapted to allow explicit consideration of treatment for SD.

Evidence of effectiveness

The literature search identified a Cochrane review on interventions for sexual dysfunction following treatments for cancer.[7] Although overall the quality of the evidence was poor, the strongest evidence was found for the use of PDE5 inhibitors following radical radiotherapy or nerve-sparing prostatectomy. Data from the four PCa studies included in the review were extracted and meta-analysed to obtain an estimate of the proportion of men benefitting from treatment (see Appendix 5). Two of the studies were in patients who had had bilateral or predominantly bilateral nerve sparing RP (Montorsi 2004,[25] Brock 2003[26]) and two following RT.(Incrocci 2001,[27] Incrocci 2006[28]) The studies report a range of different measures. The prevalence of SD is taken from Smith 2009, so a definition of success used was close to his: "erection last long enough for successful intercourse".[6]

The meta-analysis of the trials shows the change in proportion of men without SD from baseline is 26.3% for those treated with PDE5 inhibitor, and 3.8% for those given placebo, an overall treatment

benefit of 22.4%. This is the figure used in the baseline analysis. Note the Incrocci studies[27;28] could not be included in this analysis as baseline levels were not reported. An alternative analysis, including all studies, of final success proportions gave a difference of 26.5% between active treatment and placebo. See Appendix 5.

Note the trials had various exclusion criteria, most excluding comorbidities; some also older ages and previous lack of response to PDE5 inhibitors. The results in practice in the overall population of men suffering SD post treatment for RP are likely to be less than in the trials.

Application of treatment effect for ED in the model

The effectiveness trial populations of PDE5 inhibitors included men with localised cancers who had nerve sparing RP (mostly bilateral), or RT. The BAUS 2008 data showed that 46% of men who had RP had a nerve sparing procedure (unilateral or bilateral). The proportion was similar in Smith 2009, from which the rate of ED following SD was derived.[6] Smith reported a lower rate of SD following nerve sparing RP (59%) compared to non-nerve sparing procedures (80%). So the proportion of men with SD following RP who had a nerve sparing procedure is 46%*0.59/0.8 = 33.9%.

SD also affects a significant minority of men treated with AM or WW (35% not affected at baseline, Smith 2009,[6] 33% Hoffman 2003[29]). The reason for this is not clear, but may reflect these patients progression to HT, or may be due to psychological effects. It is assumed in the model that SD treatment in these patients is not effective, but the question as to whether the SD rates reported in studies reflect AM/WW alone or additional treatment is addressed with a sensitivity analysis setting the rate of SD in this population to zero.

It is assumed in the model that all men affected by ED following radical treatment (with the exception of those undergoing non-nerve-sparing RP) opt to try treatment, and that if treatment is successful patients remain on treatment and it continues to be similarly effective until disease progression (when hormone therapy is initiated) or death.

Analysis of Prescription Cost Analysis (PCa) Data 2011 shows that of all drugs prescribed for erectile dysfunction PDE5 inhibitor tablets comprised 97%, and costs have been estimated assuming their use.[30] Based on data from the Prescription Cost Analysis Data 2011 the mean cost per tablet is £5.36, and it has been assumed that one tablet per week is used.[31] Note although the PCa data is 2011 the

costs per tablet are the same as those in the BNF 2012.[24] Two GP appointments per year were also included in the costs. The costs of trial of therapy have not been included.

2.2.3 Sensitivity analysis

The model was run with the three different scenarios from the epidemiological model assuming different PSA test sensitivities (0.6 baseline, 0.4 and 0.8). Univariate sensitivity analysis was undertaken to represent particularly uncertain parameters in the screening impact model, and those likely to have the greatest effect on incremental QALYs, the latter being the primary outcome of interest. Given there is some uncertainty in the appropriate discount rate for future benefits, especially when the intervention has effects over many years a sensitivity analysis was undertaken with benefits discounted at 1.5% (baseline costs and benefits both discounted at 3.5%).

3.0 Results

Four policy options have been investigated:

- Policy 1 - A single screen at age 50 years,
- Policy 2 – Screening every 4 years from age 50 to 74 years,
- Policy 3 – Screening every 2 years from age 50 to 74 years,
- Policy 4 – Screening every year from age 50 to 74 years.

The results for these policy options are presented for the three scenarios of PSA test sensitivity.

3.1 Screening policy results

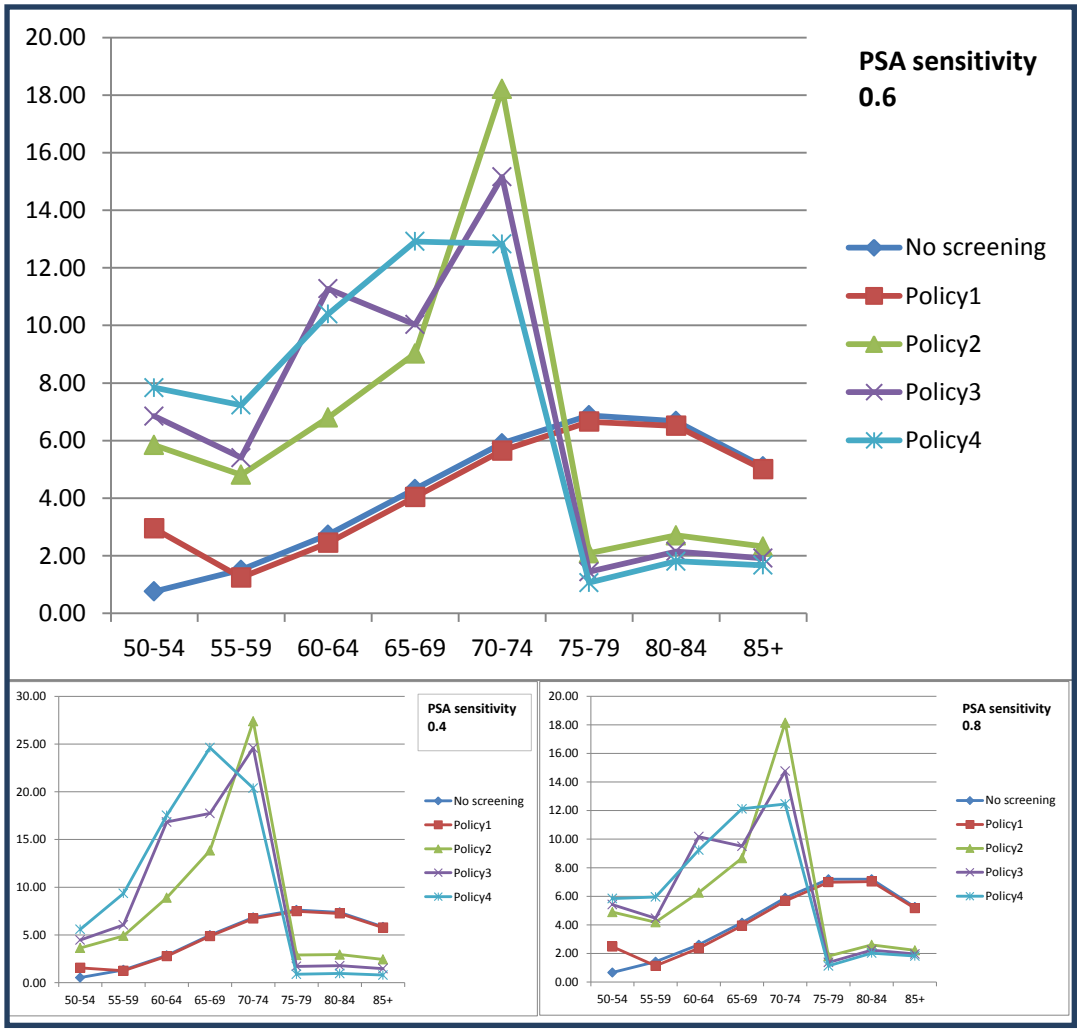
Figure 1 gives the impact of screening on the age specific incidence of prostate cancer for the four screening options under consideration. Two key results emerge from an examination of the age specific cancer incidence for all PSA sensitivities considered:

- the policy of a single screen at age 50 has little impact on cancer incidence in the longer term,
- screening every year has little marginal impact on age specific incidence over and above two yearly screening.

Table 4 presents the estimated impact of the primary screening policies on the identification and diagnosis of prostate cancer. Overdetection is defined as detection of prostate cancers in people who would otherwise have died of other causes without a symptomatic or clinical diagnosis of prostate cancer. Detection of potentially relevant cancers is defined as screen detection of cancers that would have been clinically diagnosed at some point in the future. Note this measure includes people with screen detected PCa who would otherwise have been clinically diagnosed but would have still died of other causes.

The lifetime probability of PCa is estimated at 11%, with screening screening every four years increasing it to between 18% and 22% depending on the sensitivity of the PSA test. Note that the scenario with a low PSA sensitivity results in a greater lifetime probability of cancer particularly in the more frequent biennial and annual screening policies. This is an impact of the calibration of the model to the 4 yearly screening data in the ERSPC trial, whereby the observed screening results may be associated with a low sensitivity and higher PCa prevalence or conversely a high sensitivity and lower prevalence.

Figure 1 **Screening and the age specific incidence of PCa.**



The proportion of screen detected PCa that is classed as overdetection is estimated to be in the region 50% in the baseline scenario for the repeat screening policies. The overdetection ranges between 40%and 60% for the equivalent policies depending on scenario.

The one off screen at age 50 is associated with a mean lead time for potentially relevant cancers of between 15 and 18 years, whilst for the repeat screen policies this figure is in the range 8 to 10 years.

For the four yearly screening policy the baseline average life years gained for people invited for screening is 0.08 years (29 days), this figure is estimated to vary between 20 and 67 days for the repeat screening policies. The single screen at 50 years is estimated to result in between 2 and 4 extra days life on average.

Table 4 Impact of screening on PCa identification

	PSA sensitivity 0.4					PSA sensitivity 0.6					PSA sensitivity 0.8				
Screening Policy	No screening	Once at 50	50-74 every 4 years	50-74 every 2 years	50-74 every year	No screening	Once at 50	50-74 every 4 years	50-74 every 2 years	50-74 every year	No screening	Once at 50	50-74 every 4 years	50-74 every 2 years	50-74 every year
Lifetime probability of Pca	11.0%	11.3%	22.2%	25.2%	27.2%	11.1%	11.5%	19.3%	20.6%	21.5%	11.1%	11.4%	18.2%	19.0%	19.4%
Proportion of people screen detected with PCa who would have died of other causes (Overdetection)		44%	64%	63%	63%		33%	53%	52%	52%		28%	47%	46%	46%
Proportion of people screen detected who would have been diagnosed later with clinical PCa (Potentially relevant)		56%	36%	37%	37%		67%	47%	48%	48%		72%	53%	54%	54%
Mean lead time for PCa diagnosis in potentially relevant cases (yrs)		18.2	9.2	9.7	10.2		15.9	8.5	9.0	9.3		15.2	8.2	8.5	8.8
Average life years gained per person invited for screening		0.01	0.11	0.15	0.18		0.01	0.08	0.10	0.12		0.01	0.05	0.07	0.07
Average days gained		3.5	38.8	54.3	67.4		4.0	29.2	37.1	42.9		2.2	19.9	24.0	26.6

Tables 5.1-5.3 present the distribution of stage and grade at diagnosis for screen and clinically detected PCa for a 2010 UK cohort of men aged 50 followed through for life for the three scenarios of PSA sensitivity. Whilst screening increases the overall number of PCa cases diagnosed, both the absolute number and proportion of cases detected in the metastatic state are decreased for all screening policies, with the four yearly policy (baseline scenario) resulting in a fourfold reduction from approximately 3700 cases to 950 cases estimated. In contrast the number of cases of local disease diagnosed is estimated to increase from around 29000 to over 70000 for the equivalent screening policy. This pattern is repeated although exaggerated for the more frequent screening policies.

Figure 2 presents the age specific prostate cancer mortality achieved under the different screening options together with the results for no screening. It can be seen that despite the earlier detection of prostate cancer demonstrated for screening the consequent impact on prostate cancer mortality is estimated to be negligible for the one off screen at 50 and that reduced PSA sensitivity is associated with increased effectiveness in the more frequently screened policies.

Table 5.1 Stage and grade at diagnosis of prostate cancer for a UK 2010 cohort of 50 year old men.

PSA sensitivity 0.6								
No screening	Local		Locally advanced		Mets		Total	
G<7	13792	30.5%	5514	12.2%	1599	3.5%	20904	46.2%
G=7	10317	22.8%	4938	10.9%	--	--	15255	33.7%
G>7	4733	10.5%	2272	5.0%	2122	4.7%	9128	20.2%
Total	28842	63.7%	12723	28.1%	3721	8.2%	45287	100.0%
Once at 50	Local		Locally advanced		Mets		Total	
G<7	15349	32.6%	5246	11.1%	1459	3.1%	22055	46.9%
G=7	11099	23.6%	4698	10.0%	--	--	15798	33.6%
G>7	5084	10.8%	2163	4.6%	1949	4.1%	9196	19.5%
Total	31533	67.0%	12107	25.7%	3409	7.2%	47048	100.0%
50-74 every 4 years	Local		Locally advanced		Mets		Total	
G<7	38175	48.3%	2976	3.8%	321	0.4%	41472	52.4%
G=7	23013	29.1%	2412	3.1%	--	--	25425	32.2%
G>7	10438	13.2%	1109	1.4%	629	0.8%	12176	15.4%
Total	71626	90.6%	6497	8.2%	950	1.2%	79074	100.0%
50-74 every 2 years	Local		Locally advanced		Mets		Total	
G<7	42451	50.2%	2044	2.4%	186	0.2%	44681	52.8%
G=7	25514	30.2%	1697	2.0%	--	--	27211	32.2%
G>7	11571	13.7%	781	0.9%	347	0.4%	12699	15.0%
Total	79536	94.0%	4522	5.3%	533	0.6%	84591	100.0%
50-74 every year	Local		Locally advanced		Mets		Total	
G<7	45140	51.3%	1339	1.5%	128	0.1%	46607	53.0%
G=7	27169	30.9%	1142	1.3%	--	--	28311	32.2%
G>7	12323	14.0%	526	0.6%	208	0.2%	13057	14.8%
Total	84632	96.2%	3007	3.4%	336	0.4%	87975	100.0%

Note: Gleason grade 7 and >7 are merged for metastatic cancer

Table 5.2 Stage and grade at diagnosis of prostate cancer for a UK 2010 cohort of 50 year old men.

PSA sensitivity 0.4

No screening	Local		Locally advanced		Mets		Total	
G<7	14111	31.4%	5558	12.4%	1757	3.9%	21426	47.7%
G=7	9272	20.7%	4807	10.7%	--	--	14079	31.4%
G>7	4614	10.3%	2402	5.4%	2376	5.3%	9392	20.9%
Total	27996	62.4%	12768	28.4%	4133	9.2%	44897	100.0%
Once at 50	Local		Locally advanced		Mets		Total	
G<7	15370	33.1%	5404	11.7%	1684	3.6%	22458	48.4%
G=7	9762	21.1%	4676	10.1%	--	--	14438	31.1%
G>7	4849	10.5%	2337	5.0%	2286	4.9%	9472	20.4%
Total	29981	64.7%	12417	26.8%	3970	8.6%	46368	100.0%
50-74 every 4 years	Local		Locally advanced		Mets		Total	
G<7	48076	52.8%	3622	4.0%	548	0.6%	52246	57.3%
G=7	22761	25.0%	2638	2.9%	--	--	25399	27.9%
G>7	11081	12.2%	1315	1.4%	1087	1.2%	13483	14.8%
Total	81918	89.9%	7575	8.3%	1634	1.8%	91127	100.0%
50-74 every 2 years	Local		Locally advanced		Mets		Total	
G<7	57473	55.5%	2558	2.5%	249	0.2%	60280	58.3%
G=7	26827	25.9%	1808	1.7%	--	--	28635	27.7%
G>7	13046	12.6%	900	0.9%	605	0.6%	14552	14.1%
Total	97346	94.1%	5266	5.1%	855	0.8%	103466	100.0%
50-74 every year	Local		Locally advanced		Mets		Total	
G<7	63781	57.2%	1540	1.4%	88	0.1%	65409	58.7%
G=7	29741	26.7%	1093	1.0%	--	--	30834	27.7%
G>7	14463	13.0%	544	0.5%	254	0.2%	15262	13.7%
Total	107985	96.8%	3177	2.8%	342	0.3%	111505	100.0%

Note: Gleason grade 7 and >7 are merged for metastatic cancer

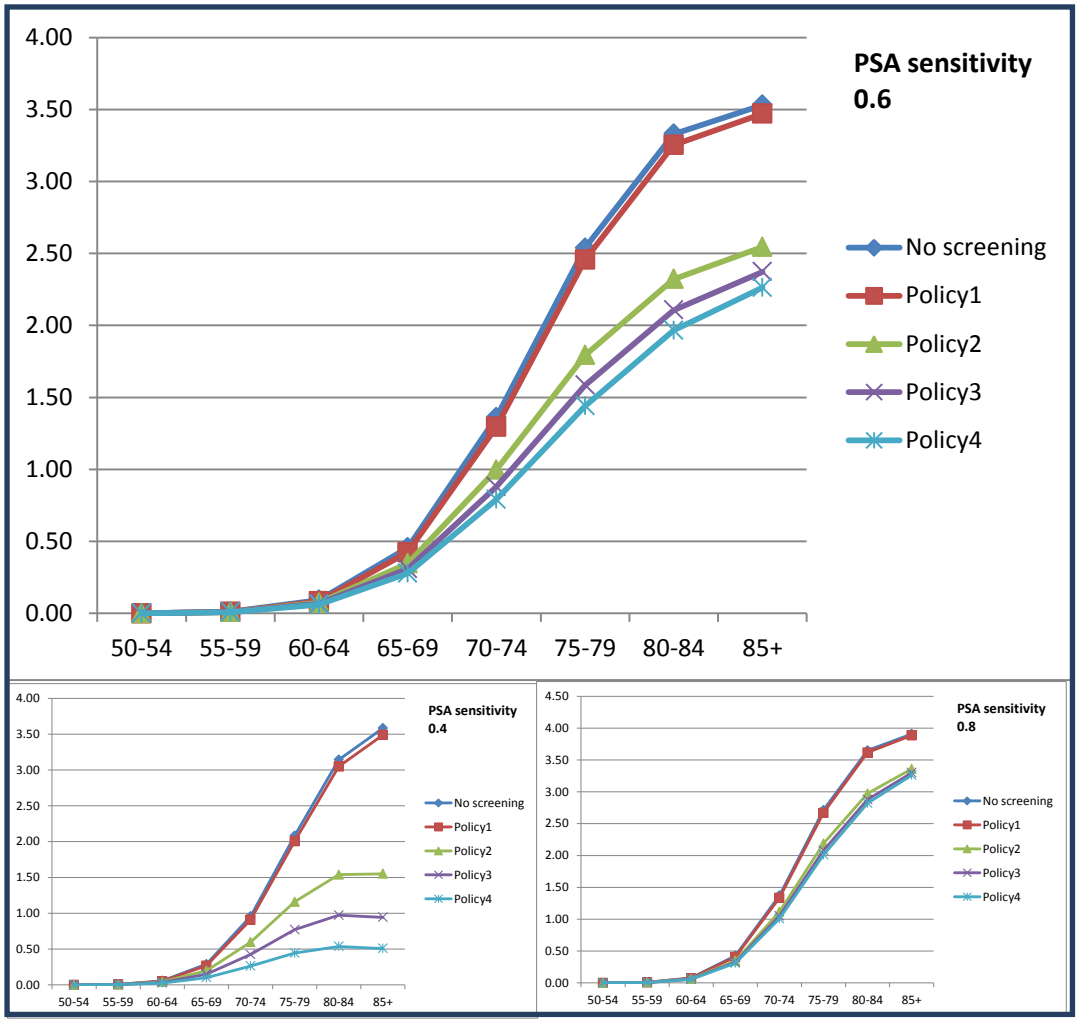
Table 5.3 Stage and grade at diagnosis of prostate cancer for a UK 2010 cohort of 50 year old men.

PSA sensitivity 0.8

No screening	Local		Locally advanced		Mets		Total	
G<7	13887	30.5%	5318	11.7%	1795	3.9%	21000	46.1%
G=7	9926	21.8%	4861	10.7%	--	--	14787	32.5%
G>7	4859	10.7%	2386	5.2%	2486	5.5%	9731	21.4%
Total	28671	63.0%	12566	27.6%	4281	9.4%	45518	100.0%
Once at 50	Local		Locally advanced		Mets		Total	
G<7	15226	32.5%	5078	10.9%	1647	3.5%	21951	46.9%
G=7	10487	22.4%	4650	9.9%	--	--	15136	32.3%
G>7	5120	10.9%	2284	4.9%	2306	4.9%	9710	20.7%
Total	30833	65.9%	12011	25.7%	3953	8.4%	46797	100.0%
50-74 every 4 years	Local		Locally advanced		Mets		Total	
G<7	37700	50.5%	2579	3.5%	291	0.4%	40570	54.4%
G=7	20453	27.4%	2089	2.8%	--	--	22542	30.2%
G>7	9789	13.1%	1028	1.4%	711	1.0%	11527	15.4%
Total	67942	91.0%	5696	7.6%	1002	1.3%	74640	100.0%
50-74 every 2 years	Local		Locally advanced		Mets		Total	
G<7	40687	52.2%	1706	2.2%	192	0.2%	42585	54.7%
G=7	22139	28.4%	1450	1.9%	--	--	23589	30.3%
G>7	10600	13.6%	715	0.9%	405	0.5%	11719	15.0%
Total	73426	94.3%	3870	5.0%	597	0.8%	77893	100.0%
50-74 every year	Local		Locally advanced		Mets		Total	
G<7	42462	53.2%	1103	1.4%	154	0.2%	43718	54.8%
G=7	23213	29.1%	975	1.2%	--	--	24188	30.3%
G>7	11121	13.9%	481	0.6%	265	0.3%	11867	14.9%
Total	76796	96.3%	2559	3.2%	419	0.5%	79774	100.0%

Note: Gleason grade 7 and >7 are merged for metastatic cancer

Figure 2 Age specific prostate cancer mortality



Tables 6.1-6.3 present summary estimates of the impact of screening on duration of PCa management and life years gained for a cohort of men aged 50 (with no PCa previously diagnosed) for each potential screening programme followed up for life. It can be seen that for the baseline PSA sensitivity of 0.6 a policy of screening every four years between the age of 50 and 74 each person screened could expect to subsequently receive 3.2 years of management for prostate cancer, and could expect to gain 0.08 years (25 days) of life from avoided or delayed prostate cancer mortality. This is equivalent to receiving on average 25 additional years of management for prostate cancer for each life year gained.

It is noteworthy that the policy of a single screen at age 50, the least effective policy from the point of view of the long term impact on overall population cancer incidence and mortality rates, is perhaps the best policy from the point of view of the individual with the lowest expected additional management years. This is because cancers screen detected at age 50 would have a greater

likelihood of arising clinically at some point in the future, there is thus a greater potential to benefit from screening, however these summary statistics do not account for the occurrence of adverse events associated with treatment and specifically do not account of the different marginal impact of adverse events associated with prostate cancer management in the younger age groups. These trade-offs are explored further in the following chapter.

Table 6.1 Impact of screening on duration of PCa management and life years gained for a UK 2010 cohort of men aged 50 not previously diagnosed with PCa.

	PSA sensitivity 0.6				
Screening Policy	No screening	Once at 50	50-74 every 4 years	50-74 every 2 years	50-74 every year
Total invited		411200	411200	411200	411200
Total screened at least once		328960	328960	328960	328960
Total PCa diagnosed	45538	47187	79307	84841	88235
Clinically detected cancers (age>=50)	45538	42238	15401	9612	5998
Total potentially relevant cancers screen detected		3300.5	30137.3	35926.5	39540.2
Total overdetected cancers		1649.0	33769.0	39303.0	42696.8
Total years of PCa management in cohort	490499	137479.1	309317.5	353518.5	383497.3
Management years per PCa diagnosed	10.8	12.4	16.6	17.7	18.5
Management years per person eligible for screening	1.19	1.42	3.20	3.66	3.97
Marginal management years per person		0.23	2.01	2.47	2.78
Total life years gained in cohort		4503.3	33041.6	41974.4	48420.0
Average life years gained		0.01	0.08	0.10	0.12
Average extra years management per life year gained		21.1	25.0	24.2	23.6

Table 6.2 Impact of screening on duration of PCa management and life years gained for a UK 2010 cohort of men aged 50 not previously diagnosed with PCa.

	PSA sensitivity 0.4				
Screening Policy	No screening	Once at 50	50-74 every 4 years	50-74 every 2 years	50-74 every year
Total invited		411200	411200	411200	411200
Total screened at least once		328960	328960	328960	328960
Total PCa diagnosed	45088	46438	91265	103622	111673
Clinically detected cancers (age>=50)	45088	43402	19252	11201	5464
Total potentially relevant cancers screen detected		1686.0	25836.2	33887.4	39624.3
Total overdetected cancers		1349.7	46176.3	58533.5	66584.3
Total years of PCa management in cohort	502182	134056.8	358000.8	440227.2	503376.9
Management years per PCa diagnosed	11.1	12.3	16.7	18.1	19.2
Management years per person eligible for screening	1.22	1.39	3.70	4.55	5.21
Marginal management years per person		0.16	2.48	3.33	3.98
Total life years gained in cohort		3924.9	43753.3	61234.4	76082.4
Average life years gained		0.01	0.11	0.15	0.19
Average extra years management per life year gained		17.3	23.3	22.4	21.5

Table 6.3 Impact of screening on duration of PCa management and life years gained for a UK 2010 cohort of men aged 50 not previously diagnosed with PCa.

	PSA sensitivity 0.8				
Screening Policy	No screening	Once at 50	50-74 every 4 years	50-74 every 2 years	50-74 every year
Total invited		411200	411200	411200	411200
Total screened at least once		328960	328960	328960	328960
Total PCa diagnosed	45726	46904	74811	78071	79956
Clinically detected cancers (age>=50)	45726	42640	13309	8473	5642
Total potentially relevant cancers screen detected		3085.9	32417.7	37253.3	40084.0
Total overdetected cancers		1178.0	29084.4	32345.0	34230.2
Total years of PCa management in cohort	475673	129260.1	281147.8	310253.2	328484.2
Management years per PCa diagnosed	10.4	11.7	16.0	16.9	17.5
Management years per person eligible for screening	1.16	1.34	2.91	3.21	3.40
Marginal management years per person		0.18	1.75	2.05	2.24
Total life years gained in cohort		2494.9	22523.4	27069.7	30022.9
Average life years gained		0.01	0.05	0.07	0.07
Average extra years management per life year gained		29.8	32.0	31.2	30.7

3.2 Impact of screening on treatment

Table 6 shows the distribution of initiation on to treatments by age for no screening. Note patients will progress to hormone therapy if they develop advanced disease, so some men will have more than one treatment. The model slightly underestimates the number of men currently having RP (6,540 – see section 2.2.2), but closely matches the expected number of radical RT (14,380 - section 2.2.2) Note no data was available to distinguish between active monitoring and watchful waiting, so the allocation between them by age is a model assumption. Note for the original model there was no total RT data available to use for calibration, and as a result RT was likely underestimated (total 5300 at baseline).

Table 6 Initiation on to treatments by age - no screening

Age band	Radical prostatectomy	Radical radiotherapy	Radical radiotherapy & HT	Hormone Therapy	Active monitoring	Watchful waiting
50 - 54	614	240	422	305	233	0
55 - 59	944	410	780	649	434	0
60 - 64	1140	420	1265	1123	383	0
65 - 69	1943	713	2346	2231	653	0
70 - 74	551	448	3073	3792	0	1324
75 - 79	601	481	3106	4049	0	1346
80 - 84	0	0	280	4937	0	2055
85 - 89	0	0	161	3081	0	943
90+	0	0	76	1823	0	514
Total	5793	2713	11508	21989	1703	6183

Figures 3.1-3.5 show how the distribution of initiation on to the different principal treatments for prostate cancer varies according to screening policy.

Figure 3.1 Radical prostatectomy - distribution with age according to screening policy

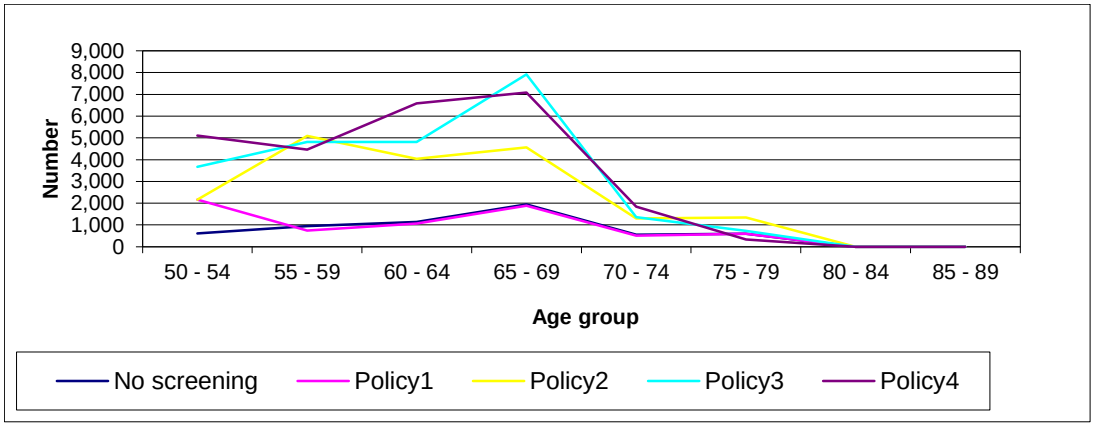


Figure 3.2 Radical radiotherapy - distribution with age according to screening policy

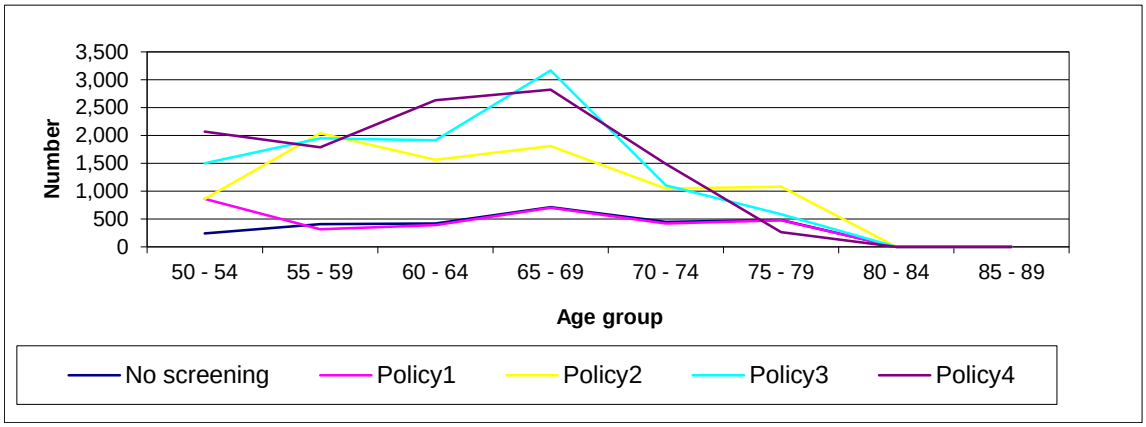


Figure 3.3 Radical radiotherapy with hormone therapy – distribution with age according to screening policy

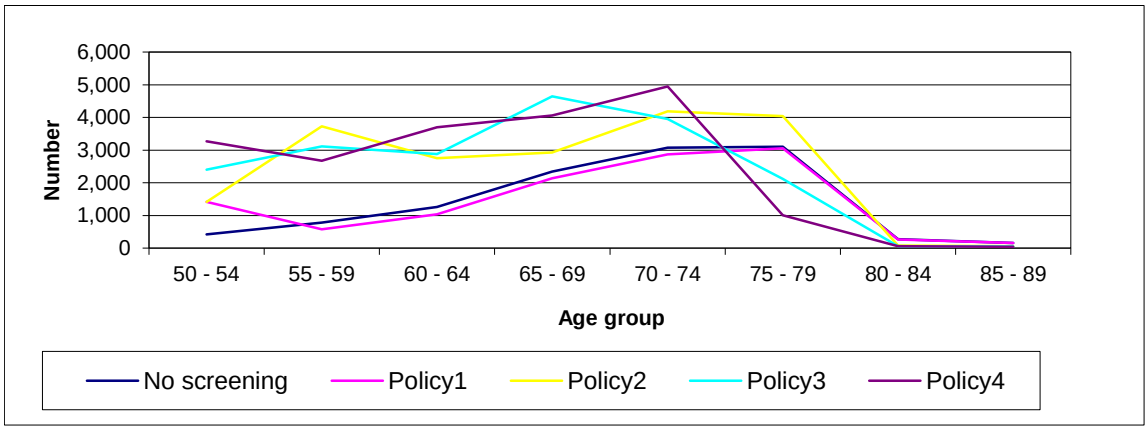


Figure 3.4 Active monitoring/Watchful waiting – distribution with age according to screening policy

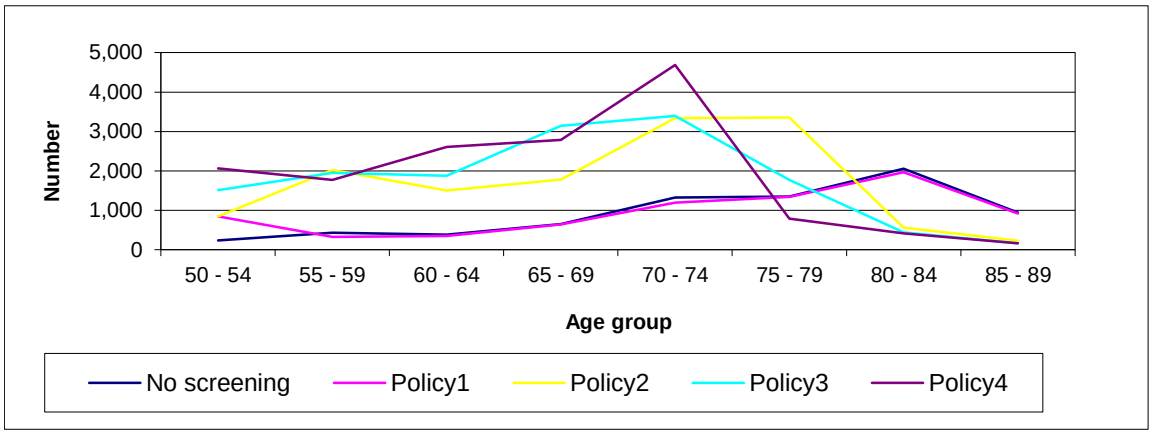
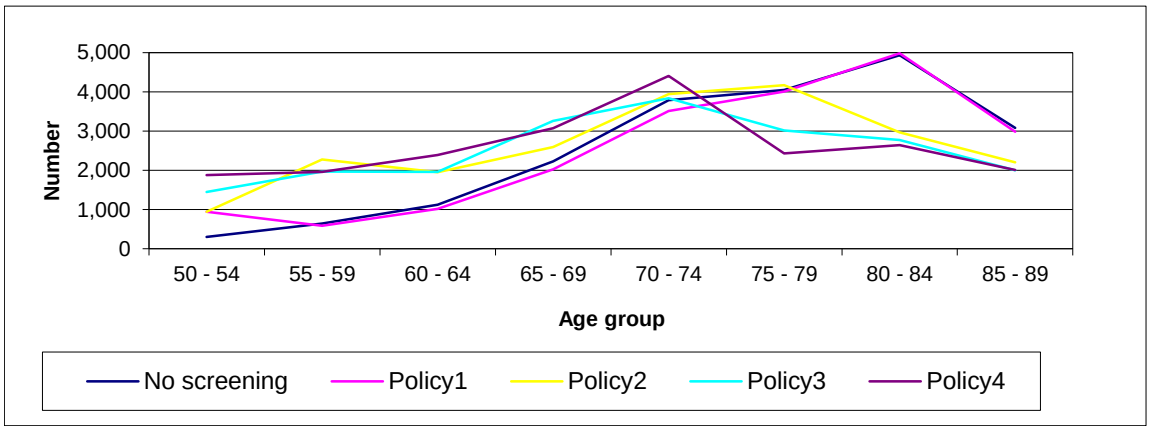


Figure 3.5 Hormone therapy - distribution with age according to screening policy



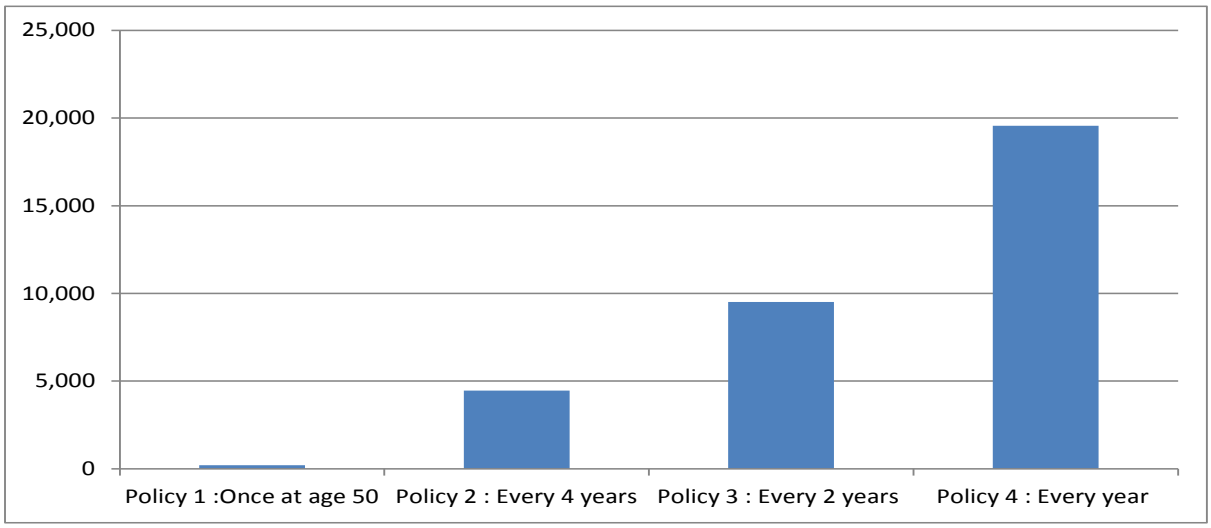
The analysis shows that screening once at age 50 (policy 1) has little effect on treatment patterns apart from a small rise in radical treatment following the screen. The more frequent the screening (policies 1 through to 4), the more radical treatment in the screened age groups. Assuming treatment patterns remain constant, radical treatment would increase up to 3 times, and over 4 times for RP, for repeat screening policies, primarily in men aged less than 75 years (Figures 3.1-3.5.) The overall number of men initiated on to HT is fairly constant over the different screening policies, but is started in younger age groups with repeat screening policies.

3.3 Impact of screening on adverse effects

Biopsy

Recent UK data has shown the risk of hospitalisation following biopsy to be 1.4%,[3] higher than that reported in the ERSPC study (0.47%), the value used previously in the model.[32] Although the risk of infection requiring hospitalisation following biopsy is still relatively low if a large number of men are biopsied as a result of screening for PCa the numbers of men admitted to hospital for infection will increase considerably from the current estimated baseline of 2,500. See Figure 4.

Figure 4 Incremental hospital admissions post-biopsy screening policies compared to no screening



Mortality from radical prostatectomy

The risk of excess mortality from surgery is small, particularly for younger men. With no screening it is estimated that a total of 25 men will die as a result of surgery, rising to 100 with annual screening.

Long term adverse effects of treatment of prostate cancer

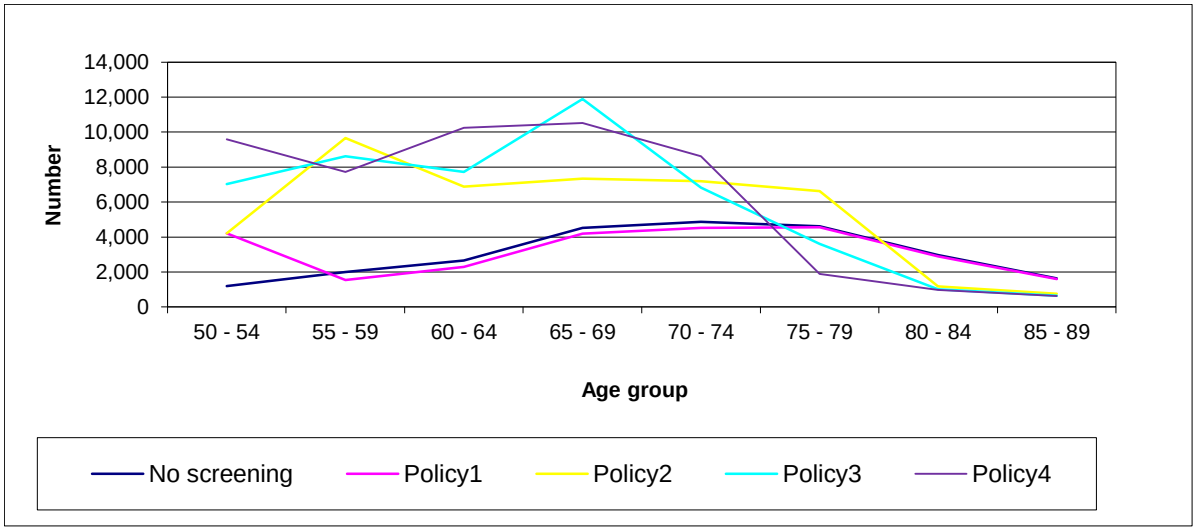
All interventional treatments for prostate cancer have adverse effects. Increasing the numbers of cancers detected through screening will result in more men suffering adverse effects of treatment, assuming treatment patterns for different age and disease stage remain the same. The model estimates the effect of different screening policies on the number of men affected by long term adverse effects of treatment for prostate cancer. Introducing screening and increasing the frequency results in increasingly more men being affected by long term adverse effects of treatment. The additional number of men affected by different adverse effects of treatment compared to no screening are shown in Table7.

Table 7 Incremental number of men affected by adverse effects of treatment for PCa screening policies compared to no screening

	Exess 30 day mortality RP	Sexual dysfunction	Urinary incontinence	Bowel complications
Policy 1 :Once at age 50	1	1,295	146	54
Policy 2 : Every 4 years from 50 - 74	47	18,928	1,785	1,342
Policy 3 : Every 2 years from 50 - 74	67	22,450	2,372	1,524
Policy 4 : Every year from 50 - 74	74	25,214	2,645	1,663

The results show an increase in all adverse events associated with PCa treatment, particularly SD, which may result from any of the treatments. The model has been careful not to overestimate the effects of PCa treatments on SD, by explicitly taking into account underlying SD in the male population, both in the incidence resulting from treatment, but also in the proportion of men that would have been affected in due course with increasing age. As well as affecting the overall incidence of adverse effects, screening policy also affects the age at which they occur. If men are treated at a younger age for PCa as a result of screening they will also incur adverse effects earlier, and have to live with them longer, as illustrated by Figure 5 for sexual dysfunction. Note the figures shown in Table 7 are the total number of men affected by SD, including those who are successfully treated. These, however, comprise a very small proportion of the total number of men affected as treatment has only been demonstrated to be effective in a minority of men treated with RT or nerve-sparing RP. Many more men develop SD as a result of HT. The effect of treatment for SD is included in the calculation of QALYs, reported below.

Figure 5 Incidence of SD by age according to different screening policies



3.4 Impact of screening on QALYs

QALYs allow differences in quality of life to be taken into consideration as well as differences in survival. Table 8 shows the effect of different screening policies on incremental QALYs compared to baseline expressed in terms of QALYs per man in the cohort (men invited for screening). The incremental QALYs reflect potential increases in overall survival resulting from screening (although the ERSPC found no statistically significant increase)[2] as well as the negative effects of harms of treatment. Table 8 shows that all screening policies result in a QALY loss compared to baseline. For policy 2, that in the ERSPC trial, the epidemiological model predicts a *lifetime* PCa death rate ratio of

0.74, and increase in overall survival of 29 days, compared to the ERSPC results of PCa death rate ratio *at 11 years follow up* of 0.79, with no statistically significant decrease in overall mortality.[2] For policies 3 (screening every 2 years) and 4 (annual screening) the model predicts lifetime PCA death rate ratios of 0.64 and 0.58 respectively, with increases in overall survival of 37 and 42 days. The differences between policies in the ratios between absolute and discounted QALYs are due to the differential changes between policies in times in different disease states, shifts in treatment due to age of diagnosis and increased survival. The discounted QALYs are more stable as they are less influenced by survival, as this occurs at the end of life, and is therefore are subject to greater discounting. A sensitivity analysis with benefits discounted at 1.5% is presented in the sensitivity analysis. Note the modelled survival gains are subject to considerable uncertainty.

Table 8 Impact of screening policies on quality adjusted life years

Policy	QALYS/per man	Discounted QALYs per man
Policy 1 :Once at age 50	0.000	-0.003
Policy 2 : Every 4 years from 50 - 74	-0.009	-0.016
Policy 3 : Every 2 years from 50 - 74	-0.001	-0.019
Policy 4 : Every year from 50 - 74	-0.005	-0.023

Scenario Analysis

Given the uncertainty in the sensitivity of the PSA test, to which the epidemiological model is senstive two further scenarios were run, with PSA sensitivity at 0.4 and 0.8, compared to the baseline value of 0.6 (see Tables 9.1-9.2).

Table 9.1 Incremental QALYs with "high" PSA sensitivity 0.8

Policy	QALYS/per man	Discounted QALYs per man
Policy 1 :Once at age 50	-0.004	-0.004
Policy 2 : Every 4 years from 50 - 74	-0.028	-0.020
Policy 3 : Every 2 years from 50 - 74	-0.017	-0.019
Policy 4 : Every year from 50 - 74	-0.023	-0.023

Table 9.2 Incremental QALYs with "low" PSA sensitivity 0.4

Policy	QALYS/per man	Discounted QALYs per man
Policy 1 :Once at age 50	-0.002	-0.003
Policy 2 : Every 4 years from 50 - 74	0.001	-0.015
Policy 3 : Every 2 years from 50 - 74	0.015	-0.017
Policy 4 : Every year from 50 - 74	0.017	-0.022

Note the PCa death rate ratio with "high" PSA sensitivity for policy 2 (equivalent to ERSPC trial) is 0.83 compared to the ERSPC result of 0.79 at 11 years follow up, so likely underestimates the benefit of screening, whereas the "low" PSA sensitivity scenario has a PCa death rate ratio of 0.54, considerably lower than that reported in the ERSPC trail.

Sensitivity analysis

Incremental QALYs are the primary outcome of interest, and is therefore the outcome used to show the results of the sensitivity analysis. Table 10 shows that with a discount rate for benefits of 1.5% (baseline both costs and benefits discounted at 3.5%) the incremental QALYs remain negative for all screening policies.

Table 10 Sensitivity analysis on QALY discount rate (1.5%)

Policy	QALYS/per man	Discounted QALYs per man
Policy 1 :Once at age 50	0.000	-0.002
Policy 2 : Every 4 years from 50 - 74	-0.009	-0.015
Policy 3 : Every 2 years from 50 - 74	-0.001	-0.013
Policy 4 : Every year from 50 - 74	-0.005	-0.018

The sensitivity analyses shown in Table 11 represent particularly uncertain parameters in the screening impact model, and those likely to have the greatest effect on incremental QALYs.

Table 11 Sensitivity analysis on screening model parameters (Incremental discounted QALYs)

Sensitivity analyses		Policy 1	Policy 2	Policy 3	Policy 4
Baseline		-0.003	-0.016	-0.019	-0.023
No HT for local G<8 (HT to WW/AM, RT+HT to RT)		-0.003	-0.012	-0.014	-0.017
Incident rate of SD for AM/WW set to 0		-0.003	-0.014	-0.016	-0.020
Urinary symptoms RP to 22% (baseline 11.2%)		-0.004	-0.017	-0.020	-0.025
Utility SD (baseline 0.90)	**0.85**	-0.006	-0.030	-0.036	-0.043
	0.95	-0.001	-0.003	-0.001	-0.003
Utility urinary (baseline 0.94)	**0.85**	-0.004	-0.019	-0.022	-0.027
	0.96	-0.003	-0.016	-0.018	-0.022
Utility bowel function (baseline 0.89)	**0.80**	-0.003	-0.016	-0.018	-0.022
	0.91	-0.003	-0.016	-0.018	-0.023
Utility hospital admission with sepsis post-biopsy (baseline 0.00)	**-0.36**	-0.003	-0.016	-0.019	-0.023
	0.23	-0.003	-0.016	-0.019	-0.023

In all scenarios the discounted QALYs remain negative, indicating that the harms from treatment outweigh the benefits. The model is particularly sensitive to the utility of SD, SD being the most common adverse effect of PCa treatment, but even if it is assumed that SD has a very small effect on mens' quality of life (utility 0.95) the incremental QALYs remain negative due to other adverse effects. The addition of treatment for SD and loss of quality of life from hospital admissions post-biopsy both had negligible effects on the results.

Note in some scenarios QALYs, prior to discounting, are positive, particularly for policies 1, 3 and 4. The only scenario where QALYs are positive for policy 2 is with the utility for SD at the maximum value, 0.95. These results however do not take into account preferences for immediate over future benefits. Furthermore it should also be noted that the occurrence of adverse events is more certain than possible increases in survival: the ERSPC reports no significant difference in all-cause mortality.

3.5 Impact of screening on resources

Routine screening for prostate cancer clearly will have a significant impact on resource use, both for screening and diagnosis of cancers, but also for the treatment or monitoring of cancers that would otherwise remain unidentified. The estimated incremental demand for different items of resource for the baseline screening policies compared to no screening are in Table 12. Note the figures show incremental resource use with time for a cohort of men aged 50. If an ongoing screening programme were introduced, once fully implemented the total additional resources required each year for the entire population of men aged over 50 could be approximated by the lifetime totals for men aged 50 (assuming the population distribution by age remains constant).

Table 12 Total incremental resource use (1000s) by screening policy compared to no screening

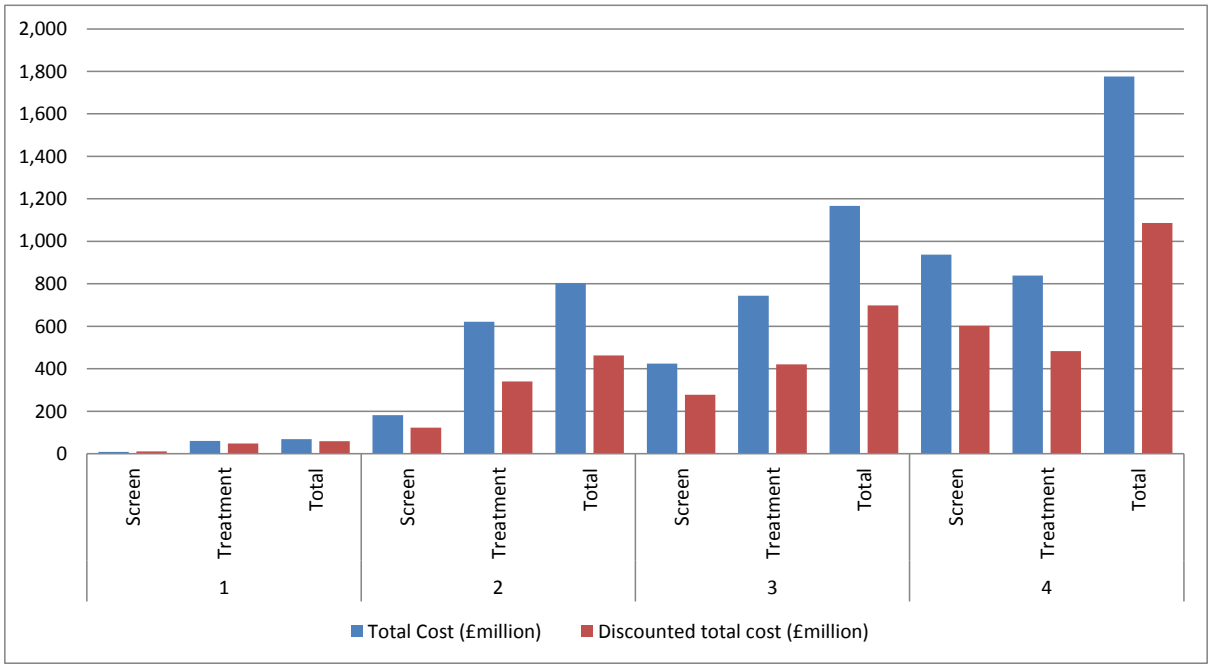
	Policy			
Resource item	**1**	**2**	**3**	**4**
General Practice Nurse	344	2,534	4,166	7,465
PSA test	420	2,899	5,895	10,375
GP appointment	-35	-26	82	473
Biopsy	15	319	680	1,398
Hospital admission (post biopsy)	0.2	4.5	9.5	19.6
Bone scan	0.20	1.89	2.10	2.30
CT scan	0.20	4.60	5.98	7.08
MRI scan	0.00	-2.71	-3.88	-4.77
Outpatient attendance	226	2,148	3,197	4,573
RP	1.17	12.71	17.50	19.61
RT planning	0.54	13.42	15.24	16.63
RT fractions	20	496	564	615
Hormone therapy (annual)	26	254	283	324
Dexa scan	12.9	124.8	138.9	159.0
Hormone refractory treatment	-0.68	-2.29	-4.28	-5.21
Terminal care	-0.37	-3.31	-4.65	-5.37

As would be expected the largest increase in resources required would be those associated with screening and diagnosis: policy 4 (annual screening) would result in 10 million more PSA tests per year and 1.4 million biopsies. The change in requirement for some resources is partially dependent on the assumptions made regarding the implementation of screening: for example it has been assumed that GP practice nurses would be responsible for taking the blood sample for a PSA test, and would give men on HT their regular injections. Whilst a large increase in many resources would be required (e.g. GP nurse sessions, PSA tests, radical treatments, outpatient appointments) there would be some small savings in others relating to the diagnosis and treatment of more advanced disease such as MRI scans, treatment for hormone-refractory cancers and terminal care.

3.6 Impact of screening on costs

Figure 6 shows the total discounted screening and treatment costs for screening policies 1 to 4 compared to no screening. Screening costs also include diagnostic tests, and treatment costs include monitoring of patients with PCa. Costs are discounted to age 50. Note these costs do not include the costs of administering a screening programme.

Figure 6 Total and discounted total screening and treatment costs for screening policies 1 to 4 compared to no screening



The total additional discounted costs of a screen once policy at 50 (policy 1) are £58 million, rising to over £1 billion for an annual screening policy. The ratio of screening to treatment costs rises with more frequent screening as the ratio of cancers detected to the number of men screened falls. With an annual screening policy (4) the costs of screening are greater than those for treatment. However the screening costs are likely to be slightly overestimated for the more frequent screening policies as the number of men screened is not adjusted for the number of men without diagnosed cancers who are monitored. Table 13 shows how the incremental costs are comprised.

Table 13 Incremental costs by screening policy and resource item (£million)

	Policy			
Resource Item	**1**	**2**	**3**	**4**
General Practice Nurse	0.00	34.24	56.29	100.85
PSA test	0.00	14.60	30.60	65.80
GP appointment	0.00	-2.71	0.65	14.74
Biopsy	0.01	114.47	244.14	501.69
Hospital admission (post biopsy)	0.00	12.00	25.59	52.58
Bone scan	0.00	0.35	0.39	0.43
CT scan	0.00	0.45	0.58	0.69
MRI scan	0.00	-0.59	-0.84	-1.03
Outpatient attendance	0.03	286.28	426.18	609.58
RP	0.01	66.69	91.87	102.92
RT planning	0.00	5.53	6.28	6.86
RT fractions	0.00	56.51	64.20	70.05
Hormone therapy	0.02	239.07	266.22	304.67
Dexa scan	0.00	9.21	10.25	11.74
Hormone refractory treatment	-0.01	-18.69	-34.93	-42.49
Terminal care	0.00	-14.69	-20.66	-23.85
Treatment for SD	0.00	0.40	0.54	0.61
Total Cost (£million)	**0.07**	**803**	**1,167**	**1,776**
Discounted total cost (£million)	**0.06**	**463**	**699**	**1,086**

The proportion of the incremental total cost comprised by each resource item varies between policies. Biopsy costs in particular vary from 8% of the total cost for Policy 1 to 28% for Policy 4. For all policies outpatient attendances are the most significant additional cost (comprising between 34%-44% of the additional costs of screening), followed by biopsies and hormone treatment.

4.0 Discussion and Conclusions

4.1 Summary of main results

Detection, stage distribution, survival and overall prostate cancer management duration.

A one off screen at age 50 years is estimated to have minimal impact on the long term incidence of PCa. However, more intensive policies can be effective in the early identification cancer, with four yearly and two yearly policies approximately doubling the lifetime risk of PCa from around 10% under no screening to around 20%. A small marginal increase in PCa identification is obtained by moving to an annual policy.

Overdetection has been defined as the detection of cancers in individuals who would otherwise have died of natural causes without a clinical diagnosis of PCa. All the repeat screening policies are estimated to entail approximately 45%-65% overdetection of PCa. Whilst the single screen policy has a lower rate of cancer detection, the overdetection rate is also reduced at around at30%-45%.

Potentially relevant cancers are defined as screen detected cancers that would otherwise arise clinically at a later date. The estimated mean lead time for potentially relevant cancers ranges from 8 to 18 years. This early detection is estimated to lead to a stage shift in cancers, with a fourfold reduction in metastatic cancers and more than doubling of local cancers.

The repeat screen policies are associated with an expected life years gained of approximately 0.05 to 0.12 years (20-67 days) for each individual invited for screening, with an equivalent figure of 0.01 (2-3 days) for the single screen policy. Whilst screening policies can often be associated with small expected gains for each individual, prostate cancer screening is also associated with an increased level of disease management, for instance for each life year gained the screening policies are associated with approximately 17-32 years of additional prostate cancer management.

The single screen at 50 policy is estimated to have a minimal impact on overall prostate cancer incidence and mortality rates, being the least effective policy in terms of relative rate of prostate cancer mortality. However, it might be considered the most attractive policy from the individual perspective as it entails the least expected excess prostate management to obtain one additional life year gained.

Treatment

The analysis shows that screening once at age 50 (policy1) has little effect on current treatment patterns apart from a small rise in radical treatment following the screen. Radical treatment in the screened age groups increases with screening intensity. The more frequent the screening (policies 1 through to 4), the more radical treatment in the screened age groups. Assuming treatment patterns remain constant radical treatment would increase up to 3 times, and over 4 times for RP, for repeat screening policies primarily in men aged less than 75 years The overall number of men initiated on to HT is fairly constant over the different screening policies, but is started in younger age groups with repeat screening policies.

Adverse effects of diagnosis and treatment

Adverse effects of the PSA test are rare and mild. Serious adverse effects of biopsy are infrequent, but nevertheless a proportion of men (1.4%) are hospitalized for infection resulting from biopsy.[32] This will result in an additional 4500 men being affected for a four yearly screening policy.

The incidence of long term adverse effects of treatment increases with screening intensity. For example the additional number of men affected by urinary incontinence compared to no screening varies from 1800 for policy 2 to 2600 for policy 4. Similarly there is up to an additional 1700 men suffering from long term bowel complications resulting from radiotherapy. By far the most common adverse effect of treatment for prostate cancer is sexual dysfunction. Regular screening with a frequency of one to four years would increase the number of men affected by between 19,000 and 25,000, depending on policy. Screening policy also affects the age at which adverse events occur. If men are treated at a younger age for PCa as a result of screening they will also incur adverse effects earlier, and have to live with them longer.

QALYs (Quality adjusted life years)

QALYs allow differences in quality of life to be taken into consideration as well as differences in survival. The net incremental QALYs reflect potential increases in overall survival resulting from screening (although the ERSPC found no statistically significant increase)[2] as well as the negative effects of harms of treatment. All screening policies result in loss of discounted QALYs: for repeat screening the loss ranges from 0.016 to 0.023 per man invited for screening. A sensitivity analysis with a discount rate for benefits of 1.5% (baseline 3.5%) also shows a loss in discounted QALYs with screening. The loss in QALYs reflects the adverse effects of treatment. Univariate sensitivity analysis showed that discounted QALYs remained negative for all of the screening policies when varying model parameters.

Resources

Routine screening for prostate cancer clearly will have a significant impact on resource use, both for screening and diagnosis of cancers, but also for the treatment or monitoring of cancers that would otherwise remain unidentified. The resources most impacted are those required for screening itself. Policy 4 (annual screening) would result in almost 10 million more PSA tests per year and 1.4 million biopsies. Whilst a large increase in many resources would be required (e.g. GP nurse sessions, PSA tests, radical treatments, hormone treatment, outpatient appointments) there would be some small savings in others relating to the diagnosis and treatment of more advanced disease such as MRI scans, treatment for hormone-refractory cancers and terminal care.

Costs

The total additional lifetime discounted costs for a cohort of men aged 50 of a screen once policy at 50 are £58 million, rising to over £1 billion for an annual screening policy. Note costs are discounted to age 50 for all policies and **do not include the costs of administering a screening programme.** The ratio of screening to treatment costs rises with more frequent screening as the ratio of cancers detected to the number of men screened falls. With an annual screening policy the costs of screening are greater than those for treatment.

4.2 Discussion

A model of the natural history of PCa has been developed and calibrated to a UK population. The model demonstrates a high degree of uncertainty in the sensitivity of the PSA test in the screening setting and thus scenario analyses are presented that examine a range of sensitivities between 0.4 and 0.8. The model is used to estimate the impact of a range of screening policies, however predicting the impact of these changes in the pattern of treatment and survival is difficult for some of the reasons discussed below.

The baseline results presented assume a PSA test sensitivity of 0.6. This scenario predicts a *lifetime* PCa death rate ratio of 0.74 for screening every 4 years, compared to the ERSPC results of a PCa death rate ratio *at 11 years follow up* of 0.79. It should be noted that the negative QALYs resulting from adverse effects of treatment are more certain than the projected gains in survival (29 days).

Whilst potential increases in survival drive increases in QALYs resulting from screening, adverse effects of treatment drive QALY losses. The latter depend on treatment modes, incidence of adverse events and the utility loss attached to adverse events.

Prediction of changes in treatment patterns resulting from different screening policies is uncertain due both to possible changes in treatment patterns arising from screening (identifying a higher proportion of very low risk tumours) and an uncertain current baseline due to the limited quality of current data. The BAUS 2008 data used in the original model still appeared to be the most reliable. However national data on RT treatment for PCa, not previously available, was used for calibration in the current model, resulting in much higher estimates of RT treatment both at baseline and for screening.

Screening will identify a greater proportion of low risk cancers which potentially may be managed with active monitoring, as indicated in the NICE guideline.[33] The recommendation that low risk cancers be managed in this way has, however proved controversial. The frequency of monitoring required, the tests that should be performed routinely and the criteria that should initiate consideration of radical treatment are also poorly defined,[34] the NICE prostate cancer guideline merely recommends that men should have at least one further biopsy.[33] The 2011 review of the guideline found no further evidence for what AM should comprise.[12]

Literature searches were undertaken to identify more recent evidence on adverse event rates and the utility of patients suffering from adverse effects of PCa treatment. The results of a recent review of PCa treatment confirmed the values used in the original model. No new literature was identified with relevant PCa state utilities. The results of a review of PCa utilities with broader inclusion criteria than used in this study are presented in the main report.[23] They indicate that the values used previously in the model are consistent with this literature.

Explicit consideration of treatment for SD was added to the latest model. However the effect on the results is insignificant. These, however, comprise a very small proportion of the total number of men affected as treatment has only been demonstrated to be effective in a minority of men following radical treatment for PCa. Many more men develop SD as a result of HT. Given recent evidence from the ProtecT study of a higher rate of hospital admission post biopsy loss of utility for these events were added to the model, but also made no difference to the results.

Despite some uncertainty in model parameters the results of different scenarios and sensitivity analyses consistently show a net loss in discounted QALYs from the implementation of PCa screening. Some analyses result in positive QALYs (i.e. no discounting). The difference arises as adverse events of treatment are incurred much earlier than survival benefits, so the latter are therefore subject to greater discounting. Sensitivity analysis with a discount rate for benefits of 1.5% also results in negative QALYs for all screening policies. It should also be noted that the occurrence of adverse events is more certain than possible increases in survival: the ERSPC reports no significant difference in all-cause mortality.[2]

The model also illustrates the increase in resources that would be required to implement a prostate screening programme. These would be significant, particularly for those associated with screening itself. A screening test with higher specificity would reduce the number of biopsies required. An analysis of patients recruited to the ProtecT trial shows that specificity may be improved by a second PSA test in selected men. The authors estimate that 61% of men would require a second test, avoiding one biopsy for every five repeated PSA tests,[35] such a strategy would be cost saving, but compliance may be an issue.

4.3 Implications for screening policy in the UK

A single screen at age 50 has little long term impact on overall age specific prostate cancer incidence and mortality rates. Intensive annual screening has little marginal benefit over a policy of screening every two years. Screening policies every two and four years are estimated to impact on early diagnosis and stage at diagnosis of prostate cancer. Cancers that would have been clinically diagnosed with background PSA testing at the level that was prevalent in 2004, would be diagnosed on average 8-16 years earlier. The two and four year screening policies are associated with overdetection rates of between 36% and 54%.

In order to obtain 1 additional year of life the modelling suggests that the repeat screening policies are associated with in the region of 22-32 years of additional prostate cancer management, with an equivalent figure of 17-30 years for the single screen at age 50 years policy. The results are consistently most positive for the scenario assuming a low PSA screening sensitivity.

Despite the impact on stage at diagnosis trials do not demonstrate any overall survival benefit from screening, this modelling suggests that overall expected survival benefit is likely to be small, in the

region of 2-4 days per person invited for screening for the single screen at 50 policy and 20-60 days for the repeat screen policies.

Assuming treatment patterns remain constant radical treatment would increase by radical treatment would increase up to 3 times for a repeat screening policy, primarily in men aged less than 75 years. The incidence of long term adverse effects of treatment (urinary symptoms, bowel function, sexual dysfunction) would rise accordingly, and shifts the incidence to younger age groups, hence increasing prevalence.

Despite predicting marginally improved survival for PCa screening policies the model shows discounted QALYs are negative for all screening policies, a result that is consistent across different scenarios and sensitivity analyses. Thus the harms of adverse effects of treatment outweigh the potential survival benefits.

Routine screening for prostate cancer clearly will have a significant impact on resource use, both for screening and diagnosis of cancers, but also for the treatment or monitoring of cancers that would otherwise remain unidentified. The resources most impacted are those required for screening itself. Policy 4 (annual screening) would result in almost 10 million more PSA tests per year and 1.4 million biopsies. Whilst a large increase in many resources would be required (e.g. GP nurse sessions, PSA tests, radical treatments, outpatient appointments) there would be some small savings in others relating to the diagnosis and treatment of more advanced disease.

The total additional discounted costs of a screen once policy at 50 are £58 million, rising to over £1 billion for an annual screening policy. Note costs are discounted to age 50 for all policies and **do not include the costs of administering a screening programme.** The ratio of screening to treatment costs rises with more frequent screening as the ratio of cancers detected to the number of men screened falls. With an annual screening policy (4) the costs of screening are greater than those for treatment.

Appendix 1 Description of model structure

A The natural history and screening model

This description of the model is closely based upon Sections 5.2 and 5.3 of the original report modified where necessary to relate to the updated cohort model.

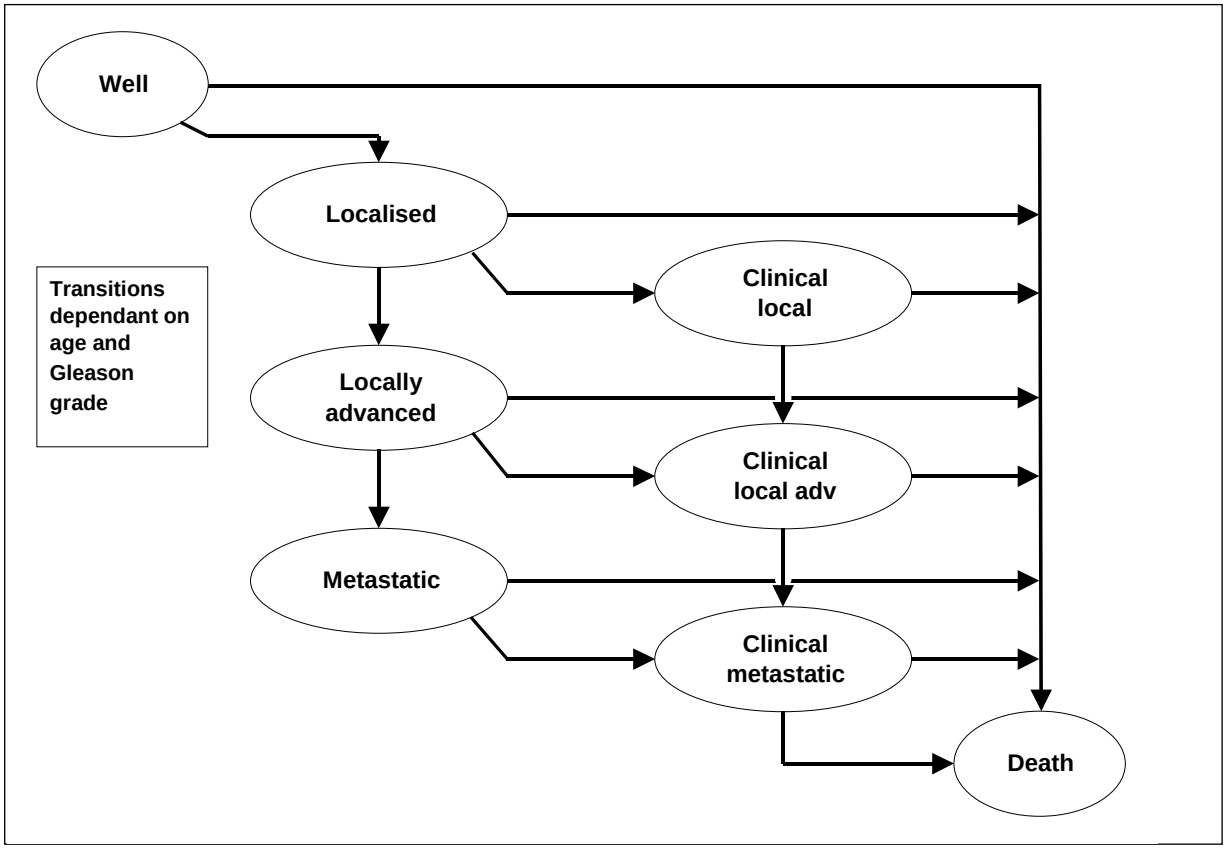
The structure of the prostate cancer natural history model is given in Figure A1.1. The model allows incidence of preclinical cancers that progress through a set of sequential disease stages; Gleason grade affects the rate of progression through local and locally advanced disease but not metastatic states. The definition of disease states is given in Table A1.1.

Table A1.1 Definition of states in model

Cancer stage categories	TNM stage
Local	T1-2; N0, NX; M0, MX
Locally advanced	T3-4; N1; M0, MX
Metastatic	Any M1

Individuals may die of other cause mortality from any state in the model and may be diagnosed clinically from any of the preclinical cancer stages. The model assumes that a proportion of individuals may develop prostate cancer at some point in their lives. For those who develop prostate cancer the first incidence age of detectable preclinical cancer is assumed to follow a Weibull distribution from birth. At onset of disease proportions of patients are assumed to develop slow medium and fast progressing cancer as characterised by the Gleason score groups G<7, G=7 and G>7, the proportions in each group are parameters within the model. The age/grade specific probabilities of transitioning out of the preclinical stages are assumed to follow Weibull distributions with the baseline estimated for the G<7 group, and G=7 group assumed to have a relative hazard compared to the G<7 group and the G>7 has a relative hazard compared to the G=7 group. The shape parameters for locally advanced and metastatic disease states are assumed to be equal.

Figure A1.1 Natural history model of prostate cancer



Individuals with prostate cancer may be diagnosed clinically at any point after onset. The model assumes that the risk of clinical diagnosis is proportional to the risk of progression to the next disease state (or PCa death for those in the metastatic disease state), but that the two processes act as competing risks. This model allows the risk of clinical detection to increase with the age and stage of the cancer and also to be related to the aggressiveness of the disease for individuals as captured by the underlying Gleason grade.

The subsequent survival of patients through to death from prostate cancer or death from other causes is included in the model. If an individual is diagnosed clinically or through screening then a relative hazard associated with treatment is applied. A common treatment relative hazard is modelled for local and locally advanced disease, with a separate relative hazard for metastatic disease. The local and locally advanced disease states are grouped here because of the availability of evidence with which to calibrate the model. The treatment of screen diagnosed cancers is modelled similarly to clinically diagnosed cancers with the exception that a different relative hazard for treatment is allowed for those individuals screen detected in the local disease state.

Disease natural history and epidemiology parameters were calibrated to the UK population using the ONS age specific cancer incidence data for 2004,[37] Eastern Region Cancer Registry stage and Gleason score distributions[38] under no screening and recruitment data from the ProtecT trial of prostate cancer treatment. (Personal communication Athene Lane, April 2010 Data from the Rotterdam section of the ERSPC trial were also used to inform the natural history parameters and PSA/biopsy test characteristics.[39,40] Differences between disease onset characteristics between the UK and Rotterdam populations were allowed by the inclusion of an adjustment parameter for the underlying time to onset of disease. UK age specific other cause mortality estimates were obtained from the ONS using data from 2004.[41] The main changes in this update were the inclusion the Schroder 2012[2] data on prostate cancer specific mortality, the exclusion of the Roemeling 2006[8] data and the inclusion of the BAUS registry data within the calibration (in the original model the BAUS registry data were used for model validation).

The best fitting sets of parameters for the three PSA sensitivity scenarios are presented in Table A1.2.

Table A1.2 Model PCa natural history parameters

	Scenario 1	Scenario 2	Scenario 3
Sensitivity of the screening test for local disease	0.40	0.60	0.80
Probability of developing prostate cancer	0.32	0.28	0.26
Age of preclinical incidence - Weibull scale	63.4	67.1	68.2
Age of preclinical incidence - Weibull ln(shape)	2.28	1.97	2.06
Probability of PCa G<7	0.59	0.53	0.55
Probability of PCa G=7 given not G<7	0.67	0.69	0.68
Dwell time in local disease for G<7	43.3	30.2	24.4
Relative hazard for G=7 compared to G<7	-0.49	-0.36	-0.51
Relative hazard for G>7 compared to G=7	-0.04	-0.02	-0.05
Age of progression from preclinical locally advanced disease - Weibull scale	43.6	42.0	44.7
Age of progression from preclinical locally advanced and metastatic disease - Weibull ln(shape)	1.57	1.72	1.80
Age of progression from preclinical metastatic disease - Weibull scale	42.0	35.3	39.9
Probability of progression to local clinical disease	0.56	0.61	0.59
Probability of progression to locally advanced clinical disease	0.70	0.75	0.71
Probability of progression to metastatic clinical disease	0.05	0.11	0.08
Relative sensivity of screening test for locally advanced and metastatic disease	0.00	0.33	0.13
Relative hazard of treatment in clinically detected local and locally advanced disease	0.01	0.00	0.05
Relative hazard of treatment in metastatic disease	0.00	0.01	0.00
Relative hazard of treatment of screen detected local disease	5.48	0.91	0.47

Figure A1.2 shows the age specific incidence of prostate cancer and rate of death from prostate cancer recorded in the ONS data for 2004 compared to the predicted values from the model with no organised screening. It can be seen that whilst the model fits well to the younger ages, the model underestimates incidence and mortality in men over 80 years.

Figure A1.2 Age specific incidence of prostate cancer

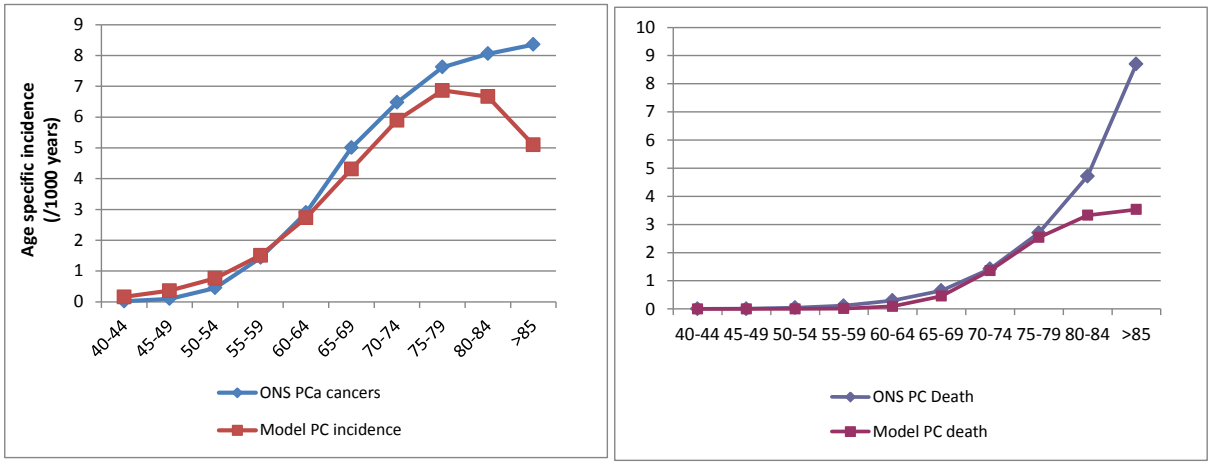


Table A1.3 gives the estimates obtained from the model relative to the results from ProtecT trial (relative values are presented to maintain confidentiality of ProtecT) for the overall incidence of prostate cancer, age profile, stage and Gleason grade distributions. It can be seen that the model overestimates screen detection rates across all ages, however the most extreme lack of fit arises in the G=7 category where there were extremely low rates of diagnosis in the ProtecT data , in the region of 3% of local disease. This lack of fit arises from the model calibration attempting to resolve the inconsistency between the ProtecT data and BAUS registry data that shows in the region of 35% of clinically detected local disease falling in the G=7 category and approximately 30% of screen detected local disease in the ERSPC screening data .

Table A1.3 Calibration results for ScHARR model against ProtecT data

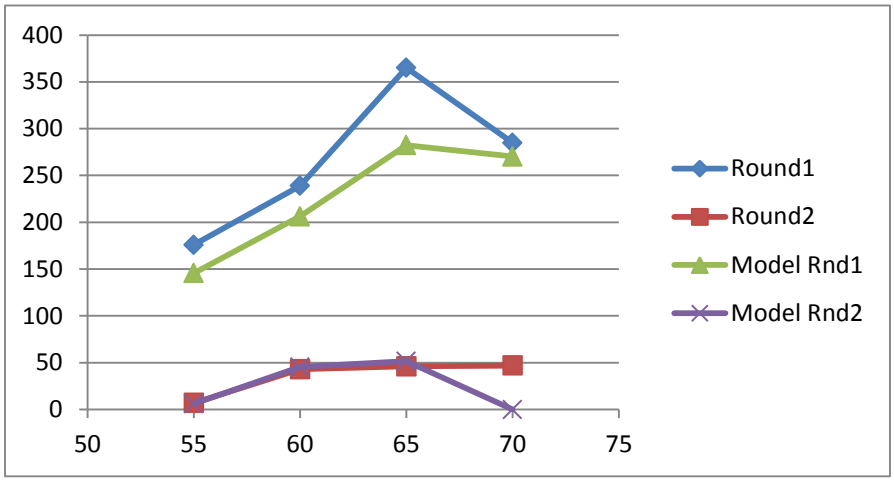
	Model relative to ProtecT data		
Total Pca	1.19		
Age at diagnosis			
50-54	1.41		
55-59	1.25		
60-64	1.09		
65-69	1.16		
Gleason grade on biopsy	Local	Locally advanced	Mets
<7	0.88	2.83	4.03
=7	12.36	1.32	--
>7	0.75	0.30	2.11

The poorer fit in prostate cancer incidence in the elderly population may arise from the structural assumptions inherent in the use of a fixed proportion of people getting prostate cancer together with the use a Weibull distribution to model time of onset of detectable disease. The original patient level model similarly exhibited a lack of fit in the older age groups, alternative model hypotheses were examined based on monotonically increasing incidence with reduced diagnosis in the over 80s, however these alternative models introduced increased complexity and little improvement in overall model fit

The Eastern Region stage distribution is matched well by the model, however the locally advanced and metastatic disease stages are grouped into an advanced category.

Figure A1.3 presents the observed and estimated screen detection rates in the first and second round of screening across the different age groups within the Rotterdam section of the ERSPC data. The model fits adequately well to this data with a slight overestimation of screen detection rates in the first round.

Figure A1.3 Age specific first and second round screen detection in the Rotterdam section of the ERSPC trial.



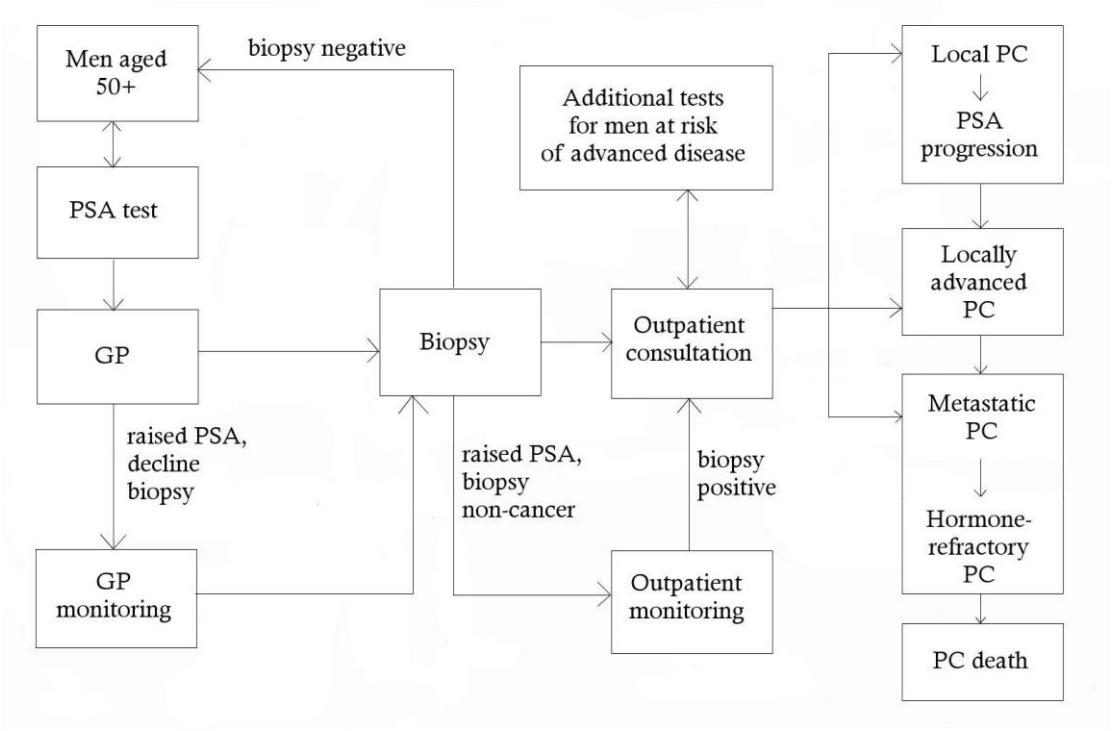
B The screening impact model

The natural history model estimates the number of cancers detected, their severity and progression through the underlying disease states of local, locally advanced and metastatic cancers. This section describes a model to assess the impact of screening, diagnosis and treatment of detected cancers on incremental resource use, costs, and harms to men from the adverse effects of treatment. Two additional states of relevance only to detected cancers are added to the natural history model: PSA progression for patients diagnosed with local disease, and hormone-refractory metastatic cancer. All men with cancers, whether diagnosed or not, are input from the natural history model, so the same number of men are included for all screening policy options. The impact model is not an individual level simulation, but treats each man as a cohort with the characteristics of the individual (age, stage of diagnosis etc.) and assigns appropriate proportions of treatment, adverse effects and resulting costs. The summation of outputs over all men show the results of different screening policies on treatment patterns, adverse effects of treatment, resource use, costs, and QALYs for the cohort of men. The screening, diagnosis and treatment pathway used in the model is shown in Figure A1.4.

The population of concern is UK men aged 50 years and over. They may currently request a PSA test, or if a screening programme were to be implemented they would be offered the test. It is assumed those who test positive would consult their GP to discuss the result and consider whether they wish to proceed to biopsy. Some men, particularly those with a relatively short life expectancy, may chose not to have a biopsy and are monitored by their GP. Most men will however have a biopsy, and

those who have a cancer identified are referred for a specialist consultation of their treatment options. Some of these men who are considered at risk of having advanced cancers (spread beyond the prostate) will be referred for additional tests to ascertain the extent of the disease. Men with a positive PSA test but cancer-negative biopsy are considered at increased risk of disease, and may be monitored including further biopsy. Men with cancer will have a range of treatment options dependent on the extent (localised, locally advanced, metastatic), and aggressiveness of their disease, as reflected by their Gleason score (G<7, G=7, G>7). Once detected, men may progress through to more advanced cancer states, eventually dying of prostate cancer, or die earlier of other causes.

Figure A1.4 The screening, diagnosis and treatment pathway



The model includes the resources and costs for the diagnosis and treatment of disease. The numbers of men who are affected by adverse effects of diagnosis or treatment are estimated, and quality-adjusted life years (QALYs) for the cohort of men calculated for each screening policy option.

All costs and QALYs were discounted at a rate of 3.5% per year[22] to age 50 using a continuous discounting function.

Appendix 2 Literature Searches

Searches were undertaken August/September 2012 for literature to inform model parameters, as shown in Tables 1 and 2.

Searches for Prostate Cancer Screening model, Table A2.1

1) Utility values for prostate cancer
2) Prevalence of sexual dysfunction in general population by age
3) Effectiveness of sexual dysfunction treatments
4) Cost effectiveness of treatments of prostate cancer at end of life/mHRPCa

Searches for Prostate Cancer Screening model, Table A2.2

5) Adverse events association with prostate cancer biopsy
6) Adverse events associated with prostate cancer treatments

Table A2.1

Details	Search type				
	1. Utility values	**2. Prevalence of SD**		**3. Effectiveness of treatments for SD**	**4. Cost effectiveness of treatments for terminal prostate cancer**
		Global	UK		
Date	2009+	2008+	2000+	2000+	2003+
Language	English	English	English	English	English
Study design	Repeat of searches from HTA monograph*	Population survey (EU) of erectile dysfunction	Erectile dysfunction in UK	Systematic review	Economic evaluation
Approach	Repeated utilities search	Keyword and title search	Keyword and title search	Systematic review search	Economic evaluation search
Sources searched	Medline Embase Cochrane Library	Medline Embase	Medline Embase	Medline Cochrane Library	NHS EED, HTA, CEA, NICE website and NIHR ERG site
Results	Medline = 333 Embase = 794 Cochrane Library = 7	Medline = 172 Embase = 72	Medline = 65 Embase = 94	Medline = 71 CDSR = 15 DARE = 29 HTA = 3 NHS EED = 8	NHS EED = 14 HTA = 17 CEA = 35 (see end) NICE website = see end NIHR ERG site = 3 (see end)
Total in Ref Man	**777**	**333**		**106**	**31**
Keywords in Ref Man	$$utility	$$prevalence		$$ed treatments	$$palliative costs

Table A2.2

Details	**5. AE PCa biopsy**	**6. AE PCa treatment**			
		Meta-analysis	Cohort	RP mortality	Hormone
Date	2006+	2008+	2008+	2006+	2009+
Language	English	English	English	English	English
Study design	Systematic review	Meta-analysis if available	Cohort study	Review	Review
Approach	Systematic review search keyword and title search	Systematic review search and terms: prostate cancer and adverse events	Citation search	Systematic review search and terms: prostatectomy and adverse events	Systematic review search and keywords: prostate cancer and androgen antagonists
Sources searched	Medline Embase Cochrane Library	Medline Embase Cochrane Library	WoS Scopus	Medline Embase Cochrane Library	Medline Embase Cochrane Library
Results	Medline = 55 Embase = 126 CDSR = 3 DARE = 0 HTA = 1	Medline = 156 Embase = 188 CDSR = 0 DARE = 10 HTA = 6 NHS EED = 2	WoS = 301 Scopus = 346	Medline = 33 Embase = 43 CDSR = 0 DARE = 3 HTA = 1 NHS EED = 1	Medline = 19 Embase = 37 CDSR = 6 DARE = 3 HTA = 1 NHS EED = 2
Total in Ref Man (unique)	**149**	**192**	**356**	**49**	**45**
Keywords in Ref Man	**$$ae biopsy**	$$adverse events **$$ae treatment reviews**	$$adverse events **$$citation $$hoffman/$$smith/$$ potosky**	$$adverse events **$$rp mortality**	$$adverse events **$$hormone treatment**

Appendix 3 Impact model parameters

Unit costs

Item	Source	Year	Cost	Inflation factor	Cost 2011/12
PSA test	Northern General Hostpital, Sheffield	2010	£11.06	1.025	£11.34
GP attendance	Curtis 2011	2010/11	£36.00	1.025	£36.92
Urology outpatient	National reference costs 2010/11	2010/11	£130.00	1.025	£133.31
Nurse (GP practice)	Curtis 2011	2010/11	£13.18	1.025	£13.51
CT scan (one area)	National reference costs 2010/11	2010/11	£95.00	1.025	£97.42
Bone scan	National reference costs 2010/11	2010/11	£181.00	1.025	£185.60
Dexa scan	National reference costs 2010/11	2010/11	£72.00	1.025	£73.83
MRI scan	National reference costs 2010/11	2010/11	£211.00	1.025	£216.37
Prostate biopsy	National reference costs 2010/11	2010/11	£350.00	1.025	£358.90
Radical prostatectomy	National reference costs 2010/11	2010/11	£5,119.00	1.025	£5,249.20
Radiotherapy	National reference costs 2010/11	2010/11	£111.00	1.025	£113.82
Radiotherapy planning	National reference costs 2010/11	2010/11	£402.00	1.025	£412.22
Goserelin Acetate 10.8 mg (every 3 months)	BNF 2012	2012	£235.00	1.000	£235.00
Hospital admission for infection following biopsy	National reference costs 2010/11	2010/11	£2,623.00	1.025	£2,689.72
Hormone refractory/metastatic annual	Collins 2005 (based on TAX327 trial)	2003/4	£6,476.32	1.259	£8,153.59
Prostate cancer death	Collins 2005 (based on TAX327 trial)	2003/5	£3,528.00	1.259	£4,441.70
ED treatment cost per tablet	Prescription Cost Analysis 2011 (BNF 2012)	2012	£5.36	1.000	£5.36

References

Curtis 2011[24], National reference costs 2010/11[4], BNF 2012[24], Collins[13], Prescription cost analysis 2011[30]

Resource use associated with the diagnosis and treatment of prostate cancer

	Resource use																
Diagnostic/ treatment item	General Practice Nurse	PSA test	GP visit	Biopsy	Hospital admission post-biopsy	Bone scan	CT scan	MRI scan	O/P appointment	RP	RT planning	RT fractions (37 per person)	Goserelin Acetate 10.8 mg (3 month)	Dexa scan	Hormone refractory treatment	Terminal care	ED tablets
PSA screening test	1	1															
Discussion of positive PSA test result			1														
Monitor men having +ve PSA test, decline biopsy (annual)		2	2														
Biopsy			0.104	1	0.014												
Additional diagnostic tests						1		1									
Monitor men with raised PSA but negative biopsy (total)				1	0.014				3								
Information Appointment									1								
Radical treatment: RP									3	1							
Radical treatment: RT									3		1	37					
Radical treatment: RT with neo-adjuvant hormone therapy									3		1	37	2				
Follow up of patients following radical treatment annual									2								
Watchful waiting annual		2	2														
Active monitoring annual				0.5	0.007				4								
Additional monitoring of patients post-PSA failure, annual						0.5	0.5		4								
Annual treatment costs for patients on HT	4								2				4	0.5			
Hormone refractory/metastatic															1		
Prostate cancer death																1	
Annual treatment for ED			2														52

Source: Clinical guideline CG58 and 2011 update,[12;42] clinical opinion, biopsy - Rosario[3]

Screening parameters

Source: ProtecT trial data (personal communication, Athene Lane, 2010)

Age group	ratio cancers/screened	% screened PSA positive	% refuse biopsy
50-54	0.014	4.3%	10.7%
55-59	0.028	8.3%	12.1%
60-64	0.051	14.4%	13.2%
65-69	0.073	19.7%	15.0%
linear extrapolation with age of ratio cancers/screened			
constant	-0.1987	-0.5071	-0.0404
age multiplier	0.004	0.0105	0.0028

Treatments for localised cancers

Age	Gleason score	RP	RT	HT	RT + HT	AM / WW
< 70	<7	37.9%	19.6%	2.6%	10.9%	29.1%
	7	41.3%	10.5%	10.2%	32.2%	5.7%
	>7	25.7%	5.0%	28.6%	38.3%	2.4%
70-79	<7	13.3%	10.6%	9.7%	22.0%	44.3%
	7	10.5%	10.3%	20.9%	44.4%	13.8%
	>7	7.8%	3.1%	44.1%	41.8%	3.2%
>= 80	<7	0.0%	0.0%	23.4%	3.4%	73.2%
	7	0.0%	0.0%	58.6%	4.7%	36.7%
	>7	0.0%	0.0%	87.1%	1.8%	11.1%
Total	<7	27.9%	15.6%	6.0%	14.1%	36.4%
	7	25.8%	9.8%	17.9%	35.4%	11.1%
	>7	13.1%	3.3%	44.7%	34.9%	4.0%
	Total	24.8%	11.4%	16.6%	25.6%	21.6%

Treatments for locally advanced cancers

Age	HT	RT + HT
< 70	43.9%	56.1%
70-79	50.9%	49.1%
>= 80	93.7%	6.3%
All	57.3%	42.7%

Sources: BAUS 2008 (personal communication Sarah Fowler, February 2010), Hospital Episode Statistics 2011-2,[9] RTDS Annual Report 2010/11,[10] see methods

It is assumed that all patients with metastatic cancers are given HT until they become hormone resistant. Time in hormone resistant disease is 1.865 years.[13]

Excess mortality post-radical prostatectomy (Alibhai 2006)[43]

Age group	Death rate
50-59	0.0018
60-69	0.0051
70-79	0.0059

Adverse effects of treatment

Treatment	Sexual dysfunction	Urinary incontinence	Bowel complications
RP	0.69	0.11	0.00
RT	0.52	0.03	0.10
HT	0.94	0.00	0.00
RT+HT	0.94	0.03	0.10
AM/WW	0.35	0.00	0.00

Source: Smith 2009,[6] Hoffman 2003,[29] Potosky 2004[44]

Underlying SD in population

Linear relationship derived.

Constant -0.532

Age multiplier 0.011

Source: Korfage 2008[45]

SD treatment

Parameter	Value	Source
Proportion successfully treated	0.224	Meta analysis: see Appendix 5
Proportion RP nerve sparing	0.46	BAUS 2008
Ratio men getting ED from NS RP/ED non NS RP	0.738	Smith 2009[6] (derived)

Utility of prostate cancer states

State	Utility	Source
Sexual dysfunction	0.90	Krahn
Urinary incontinence	0.94	Krahn
Bowel complications	0.89	Krahn
Hormone refractory metastatic disease	0.64	Sullivan

Krahn 2003,[46] Sullivan 2007[47]

Utility of patient hospitalised post-biopsy (assume sepsis) assume 0.00, Galante (sepsis associated with pneumonococcal disease) -0.295 (95% CI -0.359, 0.231).[20]

Baseline population age-related utility (Ara 2010)[48]

= constant	0.9508566
+ male	0.0212126
+ age *	-0.0002587
+ age^2 *	-0.0000332

Other parameters

Time between PSA progression and locally advanced disease 2.6 years. Derived from Kestin 2002.[49]

Discounting

All costs and QALYs discounted at 3.5% per year[22] to age 50 years.

Appendix 4 Adverse Effects of treatments for PCa

In the original model the results of two large population based cohort studies were used to estimate the prevalence of adverse effects following PCa treatment (PLCO – Hoffman 2003,[29] Potosky 2004;[44] Smith 2009[6]). These cohorts were both followed up for a few years after treatment, thereby reporting long term harms of treatment, which are of most interest in the model as they have the greatest impact on quality of life. The results of Smith were particularly relied on, being more recent than the PLCO study, including all modes of treatment including HT and AM, and reporting baseline levels prior to treatment thereby allowing the incidence of AEs in patients not affected at baseline to be estimated.

A literature search was undertaken to identify if there were any significant new studies to inform the prevalence of post-treatment harms used in the model. It identified a comprehensive systematic review of the benefits and harms of treatments for localised PCa undertaken by the U.S. Preventive Services Task Force (Chou 2011).[21] Searches were undertaken between 2002 and 2011 for published randomised and cohort studies that compared RP and RT with WW/AM and reported mortality, quality of life and harms of treatment. The review included 2 RCTs and 14 cohort studies reporting harms of treatment. The cohort studies included some reports of the two large population based cohort studies referred to in the original modelling analysis (PLCO – Hoffman 2003[29] (Note Potosky 2000, Potosky 2004[44] excluded by Chou[21] as no comparison with WW); Smith 2009[6]). The results of Chou review and meta-analyses are compared with the values used in the model.

RP mortality

Chou identified four studies reporting mortality subsequent to RP and confirms the overall rate of 0.5% previously used. [21]

Urinary symptoms

RP – The pooled analysis of one RCT and 4 cohort studies in Chou gives an absolute difference between RP and WW of +22% in the prevalence of urinary symptoms,[21] compared to that derived from Smith and used in the model of +14%. The largest study in the Chou meta-analysis was the PCOS report of Hoffman, which reports an absolute difference of +27% at 2 years post-treatment.[29] The difference is likely due to differences in definition of the urinary problem: another report of the PCOS study, using a different definition to that of Hoffman reports an absolute difference of only 6.1% with the same follow up (Potosky 2000). The Smith data will be used as before, but with a

sensitivity analysis with urinary symptoms +22% compared to AM/WW (using Smith 2009 baseline for AM/WW).

RT - 4 cohort studies found no clear increase in risk of urinary incontinence following RT compared to WW, but one small RCT did (RR 8.3, 95% CI 1.1, 63). In a pooled analysis the increase in absolute risk was 3.1% (95% CI -1.8%, 8.0%), and the RR 1.4 (95% CI 0.78, 2.4).[21] (Smith +2.7% to baseline – no change made).
HT – no difference found HT/WW in two cohort studies (Hoffman 2003[29] (PCOS), Smith 09)[21] i.e. same data us previously used – no change.[6]

Sexual Dysfunction

RP / RT The pooled analyses in Chou 2011[21] support the use of the Smith 2009 data[6] (absolute risk difference RP/WW Chou 28%, Smith 34%; RT/WW Chou 15%, Smith 17%)

HT – Chou presents data from the PCOS and Smith studies only, so there is no additional data.[21] Use Smith 2009 as before. [6][Note Chou has recalculated prevalence rates based on reported N at baseline, rather than on the number of respondents at 3 years (for Smith at least), thus assuming that prevalence of AE is zero amongst drop outs. This is not a credible assumption, and casts doubt on some results from Chou]

Rectal toxicity

The Chou review confirms that patients have more bowel bother and worse function following RT compared to WW.[21] Chou reports that two studies with longer follow up (3 and 5.6 years) found no significant differences in bowel urgency, suggesting that rectal toxicity following RT may diminish with time. (But the study with 3 yr follow up is Smith 2009 –and they report an OR of 0.58, 95% CI 0.39 to 0.86).[6] Keep 10% prevalence bowel problems, with sensitivity analysis 3.9%. (NB 10% Hoffman/Potosky, also if look at Smith difference at 3 years between RT and AM relative to baseline.)

The Chou review also found no evidence of difference in rectal toxicity between RP and WW and HT and WW, supporting the previous assumption of 0% patients affected with bowel toxicity following these treatments.[21]

Appendix 5 Effectiveness of treatment for SD following radical treatment for PCa

Study	PC treatment	N	ED treatment	Baseline success	After ED treatment	Change from baseline	N	ED treatment	Baseline success	After ED treatment	Change from baseline	Comment
Brock 2003	Nerve sparing RRP (73% bilateral nerve sparing)	146	10 mg vardenefil	0.07	0.37	0.3	145	placebo	0.06	0.1	0.04	
		149	20 mg vardenefil	0.07	0.34	0.27						
Montorsi 2004	Bilateral nerve sparing RRP	201	20mg tadalafil on demand	0.175	0.405	0.23	102	placebo	0.158	0.194	0.036	
Incrocci 2001	External beam RT	60	50mg sildenafil on demand, but most needed 100mg	not reported	0.55		60	placebo	not reported	0.18		Crossover study so total N=60
Incrocci 2001	3D CRT	60	20mg tadalafil on demand	not reported	0.48		60	placebo	not reported	0.09		Crossover study so total N=60
Population weighted averages					**0.402**	**0.263**				**0.138**	**0.038**	

References:

Brock 2003,[26]

Montorsi 2004,[25]

Incrocci 2001,[27]

Incrocci 2006.[28]

Difference treatment - placebo	Change from baseline (2 studies)	0.224
	Difference post-treatment (4 studies)	0.265

Note the studies included in the table were identified in Cochrane review (Miles 2007).[7]

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