UK National Screening Committee

Screening for Prostate Cancer

Review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

Version 1: This document summarises the work of ScHARR [1 2] and places it against the UKNSC criteria

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://www.screening.nhs.uk/policies and the policy review process is described in detail at http://www.screening.nhs.uk/policyreview

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Introduction

Since the introduction of the PSA (Prostate Specific Antigen) test in the 1980s there has been a debate as to whether older men should be routinely screened for prostate cancer. Although prostate cancer is a significant cause of death (10,000 deaths in the UK, 2006), the case for screening is not clear cut. Firstly, the test itself has poor specificity. Increased PSA levels are associated with a raised probability of prostate cancer, but many men with raised levels do not in fact have prostate cancer. Secondly, to make a diagnosis a biopsy is required which risks complications such as discomfort and bleeding, and less commonly sepsis. Thirdly, the optimum treatment of prostate cancer is uncertain. Many men have slow growing cancers that may never bother them.

Recently two trials have been published, one European the other from the US, both of which had the objective of evaluating the effect of PSA screening on death rates from prostate cancer. These two trials report apparently conflicting results. The European study (ERSPC) showed a reduced death rate ratio in the screening group compared to the control of 0.8 (95% confidence interval 0.65-0.98). However the US study (PLCO) showed no statistically significant difference in death rates between the screened and control group, but there were more prostate cancer deaths in the screened group compared to the control.

Appraisal against UK NSC Criteria[12]

1. The condition should be an important health problem

Prostate cancer is the most common cancer in men in the UK, excluding non-melanoma skin cancer. Over 34,000 cases are diagnosed every year, accounting for over a quarter of all cancer cases diagnosed in men. Prostate cancer is also the second most common cause of cancer death after lung cancer, with more than 10,200 mortalities.

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

The epidemiology of prostate cancer is an area of significant interest and widespread research, however the exact natural history and cause of the disease is still relatively unknown. Commonly accepted risk factors for prostate cancer include age, family history (genetic factors) and ethnicity. A number of other environmental factors such as life-style and socio-economic factors have also been suggested as contributing to an increased risk of prostate cancer.

The prostate is a small gland that resides in men below the bladder and in front of the rectum, which surrounds part of the urethra and is used in the production of semen. As men age the prostate gland often enlarges, a condition known as benign prostatic hyperplasia (BHP), which can cause urinary problems. However the presence of benign

or malignant tumours can also have the same symptoms such as difficulty passing urine or pain. Although BHP often occurs in association with prostate cancer, it is not thought to be a precursor of the disease.

Whilst the majority of prostate cancers are very slow growing and do not pose a threat, a significant minority of cases progress rapidly. As the exact process of disease progression is not well understood, progression can broadly be described as the development of localised organ-confined cancer, before the invasion of surrounding tissues, bones or other sites. Disease progression is however thought be related to the size and spread of the cancer and the loss of cell differentiation.

The risk of developing prostate cancer significantly increases with age. Approximately 80% of men will have cancer cells in their prostate by the age of 80. It is also recognised that the relative risk of prostate cancer increases significantly with the total number of family members diagnosed. Ethnicity is widely accepted to be an important factor in the risk an individual has of developing prostate cancer. Black men are at a significantly higher risk of developing prostate cancer regardless of their country of origin.

Factors that are less supported include life-style factors such as diet, multi-vitamin intake, sunlight exposure, job-related chemical exposure, smoking, and level of physical activity. It has also been suggested that socio-economic factors may influence the probability of developing prostate cancer or of being diagnosed with prostate cancer. This may be due to differences in the level of access to health services between social classes. Alternatively the level of education may play a part in that more educated people may be more informed and thus more likely to seek advice from a GP. Sexual activity and sexually transmitted infections have also been cited as possible risk factors.

3. All the cost-effective primary prevention interventions should have been implemented as far as practicable

N/A

4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

N/A

5. There should be a simple, safe, precise and validated screening test

There are several diagnostic techniques available for determining the presence or extent of prostate cancer, with the three main procedures used to diagnose prostate cancer being digital rectal examination (DRE), PSA blood test, and transrectal ultrasound (TRUS) – guided biopsy; however the prevalence of such tests are not well recorded or centrally monitored.

The PSA test itself has poor specificity. Increased PSA levels are associated with a raised probability of prostate cancer, but many men with raised levels do not in fact have prostate cancer. In a screening trial 76% of men with raised PSA levels had a false positive result.

6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

A PSA of 4ng/mlmmols is described as raised though in a screening trial 76% of men with raised PSA levels had a false positive result.

The age-specific cut-off PSA measurements recommended by the Prostate Cancer Risk Management Programme are as follows: aged 50−59 years ≥ 3.0 ng/ml; aged 60−69 years ≥ 4.0 ng/ml; aged 70 years and older ≥ 5.0 ng/ml [3]

7. The test should be acceptable to the population

The work of the prostate risk management programme implies that the PSA test is acceptable[4].

8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

NICE have produced guidance Prostate cancer: diagnosis and treatment: full guideline.

There is however no policy in place for men who are PSA positive, but no cancer is detected on biopsy. This group comprises ~7% of men aged 50-70[5]. These men may be monitored and have further biopsies.

9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out

N/A

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

The European trial suggests that there is benefit in prostate cancer mortality to early detection and treatment, though the balance between that and harm is the issue.

11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

Men diagnosed with cancer have a difficult decision as to what treatment to choose. Most screen detected cancers are low stage (confined to the prostate) and low grade, (indicating more indolent disease progression), and may never cause clinical symptoms in the man's lifetime. Autopsy series show prostate cancer prevalence in men aged 50 years and over to be greater than 50%, but lifetime risk of death is 3%. There is however considerable uncertainty in distinguishing indolent from aggressive cancers. Active monitoring is an option for some men, avoiding immediate radical therapy. Research is ongoing as to the optimum monitoring regimes and the criteria used to reconsider the need for radical therapy. Adverse effects of radical treatment such as sexual dysfunction and urinary incontinence are common, and may be enduring.

12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme

NICE published 'Improving Outcomes Guidance' related to Urological cancers including prostate cancer in 2002. This describes the features of a high quality clinical service. Since then, services have undergone more reconfiguration – for example to ensure that radical prostatectomy is only carried out in centres undertaking more than 50 procedures a year.

13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened

Recently two trials have been published, one European the other from the US, both of which had the objective of evaluating the effect of PSA screening on death rates from prostate cancer. These two trials report apparently conflicting results. The European study (ERSPC) showed a reduced death rate ratio in the screening group compared to the control of 0.8 (95% confidence interval 0.65-0.98). However the US study (PLCO) showed no statistically significant difference in death rates between the screened and control group, but there were more prostate cancer deaths in the screened group compared to the control.

ERSPC and PLCO Trials

2.1 Introduction to the studies

ERSPC

This trial was initiated in the 1990s, with the objective of evaluating the effect of PSA screening on death rates from prostate cancer. Men were randomised to screening or usual care. A total of 182,000 men aged between 50 and 74 were enrolled in seven study centres in different European countries. A core age group of 55-69 was pre-defined, totalling 162,243 men, and men of this age were included in all countries. The primary results presented are based on the core age group. Younger and older men were only included in some countries. The results for the complete cohort are shown in an Appendix to the main paper. A feature of this trial is that the centres in the different countries did not all adhere to the same trial intervention. As well as the differences in the age groups included in the trial there was some variation in the interval between screens, the age when screening was discontinued, the PSA cut-off value used to determine a positive test, the use of ancillary screening for borderline positive tests (e.g DRE, ratio free to total PSA, transrectal ultrasonography) and biopsy techniques. The population was derived from several countries with potentially differing underlying incidence of prostate cancer, and different levels of screening in the control population. Local policies also guided treatment of prostate cancer.

PLCO

76,693 men aged 55-74 at 10 centres in the United States were randomised to screening or usual care between 1993 and 2001. The trial evaluated the effect of PSA screening and DRE on the death rate from prostate cancer. Men with a positive PSA test *or* suspicious DRE were advised to seek diagnostic evaluation. No diagnostic or treatment protocols were applied.

Conclusions from the comparison of the ERSPC and PLCO trials

A salient difference between the two trials is the level of contamination between the screened and control cohorts. Contamination compromises the internal validity of the trials. External validity may have also been affected if the rate of screening in the control was not representative of the general population, although the changing PSA screening rates during the period of the trial may be as great an issue. In the PLCO trial, not only

was the level of ongoing screening in the control cohort greater than that for the ERSPC, but also the extent to which the study population had been screened prior to enrolment in the trial. In all comparisons between the screened and control cohorts much greater differences were seen in the cancers detected in the ERSPC trail than the PLCO.

The results indicate that in the PLCO trial there was no benefit from the additional screening given to patients in the screening arm compared to that obtained by patients in the control group. Taken together the results of the two trials are consistent with a hypothesis that some prostate cancer screening may lead to a reduction in prostate cancer mortality, but that there is an (unknown) level beyond which further screening is at best of no value. It should be noted however that, of the evidence considered, there is only a single trial which showed a reduction in mortality rate resulting from a screening programme, and that the upper limit of the 95% confidence interval around the death rate ratio (screened to control) (0.98) is close to 1.

The above discussion does not consider the adverse effects of treatment for prostate cancer, which are reported in neither trial. These adverse effects need to be balanced against any potential reductions in mortality.

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public

The work of the prostate risk management programme implies that the PSA test is acceptable[3].

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

All screening policies result in loss in quality adjusted life years (QALYs): for repeat screening the loss ranges from 1.1 to 1.4 QALYs undiscounted, or 0.3 to 0.8 discounted QALYs, per man with prostate cancer (detected or not), depending on policy. The more frequent the screening, the greater the QALY loss. The loss in QALYs reflects the adverse effects of treatment.

PSA test and DRE

The PSA test entails taking a blood sample. Adverse effects are mild (dizziness, bruising and haematoma) and extremely rare: 26.2 per 10,000 tests. DRE similarly very rarely leads to bleeding and pain (0.3 per 10,000).

Biopsy

Minor adverse events are relatively common. In a systematic review of biopsy methods rates of hematospermia were reported to be 75% and 29% respectively for 10 core biopsies, which is the current UK standard. These rates are, however, derived from a single study, and rates for 12 to 13 cores show a range of 6% -82% for hematospermia and 1% to 23% for rectal bleeding. In the ERSPC study, which used sextant biopsies, the rate of hematospermia was 50%, with 23% of patients having symptoms for more than three days. Rectal bleeding was less common at 1.3%, but the results of the Eichler review suggest that the incidence of rectal bleeding is associated with the number of biopsy cores.

Major adverse events causing significant discomfort or additional treatment are much less common. Eichler reports infection rates of 0.9% for 10 core biopsies (0.0 – 0.7% for 12/13 cores) and bleeding in 0.3-0.6 per cent of men. Infection rates will vary according to the use of antibiotic prophylaxis used. In the ERSPC study all men were given prophylaxis both prior to and post-biopsy. Of these 3.5% developed fever, and 0.47% were admitted to hospital for intravenous antibiotic therapy, and recovered within days.

Adverse effects of radical treatment such as sexual dysfunction and urinary incontinence are common, and may be enduring.

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 over 45% over detection of PCa. Over detected cases are estimated to be exposed to an average of 11-13 years of management for their PCa.

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 is also approximately 11-13 years.

The repeat screen policies are associated with an expected life years gained of approximately 0.03 years (10-11 days) for each individual accepting screening, with an equivalent figure of 0.004 (1.2 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 a high level of disease management, for instance for each life year gained the repeat screen policies are associated with approximately 67-84 years of additional prostate cancer management and 36 years for the single screen policy.

The incidence of long term adverse effects of treatment increases with screening intensity. For example, in the cohort of UK men currently aged 50 the additional number of men affected by urinary incontinence compared to no screening varies from 1400 for screening 4-yearly and over 2000 for annual screening. Similarly up to an additional 1000 men will suffer 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 20,000 to 25,000, depending on policy. There is some uncertainty in these figures arising both from current treatment patterns (and also

assumed future patterns), and dysfunction rates following treatment, but sensitivity analysis shows that even with more favourable assumptions at least 16,000 men would be affected with regular screening.

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource

It is estimated that a policy of screening men aged 50-74 every four years would cost an additional £0.8 billion per year.

The metric of incremental cost effectiveness ratio (ICER), commonly used in health economic analysis, is not applicable in these circumstances where the current situation of no screening dominates all screening options i.e. is both less costly and more effective (more QALYs).

17. All other options for managing the condition should have been considered (eg. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available

18. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards

N/A though QA for other cancer programmes would be a model

19. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

Additional patient interventions for screening policies compared with no screening

	Radical prostatectomy	Radical radiotherapy	Radical radiotherapy & HT	Hormone Therapy	Active monitoring	Watchful waiting	Other local treatment
Policy 1 :Once at age 50	377	218	1	578	317	-19	465
Policy 2 : Every 4 years from 50 - 74	7,180	4,888	1,142	14,938	5,966	1,079	9,798
Policy 3 : Every 2 years from 50 - 74	9,727	5,796	935	16,805	8,227	-1,162	11,391
Policy 4 : Every year from 50 - 74	11,171	6,186	893	17,193	9,560	-2,837	12,001

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. Assuming treatment patterns remain constant radical treatment would increase by 2.5 – 3 times for repeat screening policies, primarily in men aged less than 75 years. Repeat screening also increases the number of men treated with hormone therapy at some time in their life, but by a much lesser extent: by approximately 50% more relative to current activity.

20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice

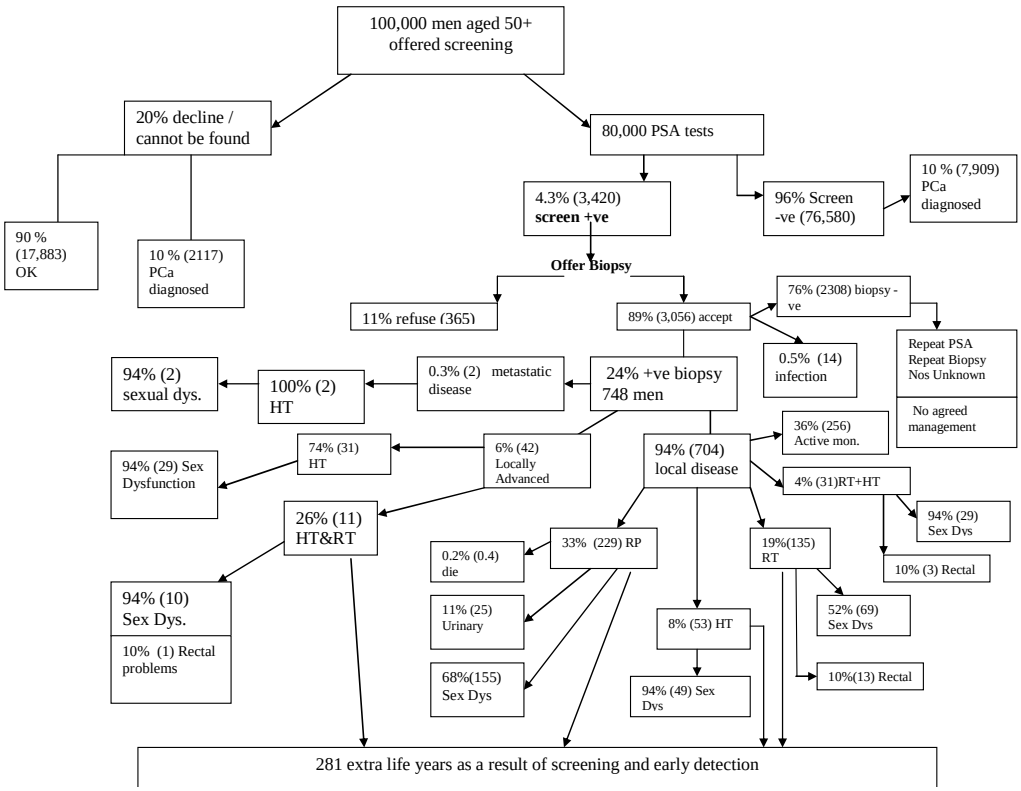
The prostate risk management programme has produced high quality field tested information on the pros and cons of screening using PSA.

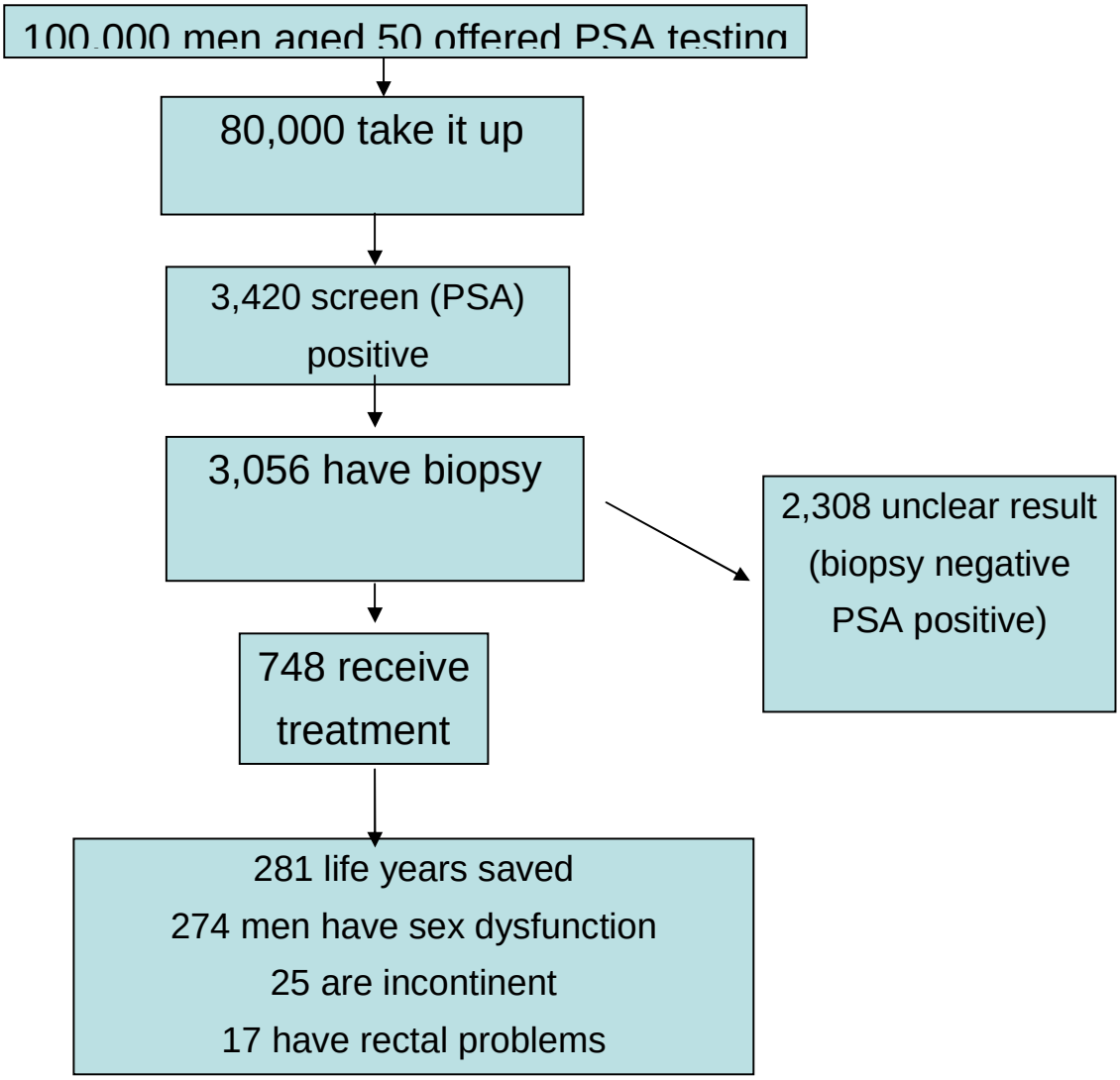
21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public

22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members

N/A

Screening flow chart




100,000 men aged 50 offered PSA testing
80,000 take it up
3,420 screen (PSA) positive
3,056 have biopsy
2,308 unclear result (biopsy negative PSA positive)
748 receive treatment
281 life years saved
274 men have sex dysfunction
25 are incontinent
17 have rectal problems

Conclusions

The harms from prostate cancer screening using PSA are currently likely to outweigh the benefits. In this circumstance screening for prostate cancer cannot be justified on the current evidence.

The main reasons are:

- PSA is a poor test for prostate cancer and a more specific and sensitive test is needed
- Currently we are unable to correctly identity those cancers which will progress and those which are indolent and may be safely watched.
- The data relating to incidence prevalence and treatments is poor and renders planning very difficult.

Implications for policy

Although cancer registries collect data on all new cases of prostate cancer, the quality of the associated data on staging, co morbidity, pathological grade and primary treatment is poor. This needs to be rectified in order to assist in understanding and modelling the likely impact of changing testing and treatment regimes for prostate cancer

Implications for research

Prognostic assessment of prostate cancers to more accurately differentiate aggressive cancers from the indolent ones.

Treatment effectiveness for different prognostic groups particularly for the early stage cancers detected by screening: outcomes to include progression to advanced disease states and mortality)

Developing treatments for all disease states with less severe adverse effects.

Developing a more specific test for prostate cancer

Measurement of HRQoL in UK men with prostate cancer, by treatment mode, preferably using the EQ-5D instrument (as recommended by NICE)

References

[1] Option appraisal: screening for prostate cancer; *Preliminary Report (1) to the National Screening Committee* July 2009. Silvia Hummel, Jim Chilcott, Matthew Mildred. School of Health and Related Research (ScHARR)

[2] Option appraisal: screening for prostate cancer. Report to the UK National Screening Committee. March 2010 Silvia Hummel, Jim Chilcott, Matthew Mildred. School of Health and Related Research (ScHARR)

[3] (NICE Clinical guideline 27, 2007).

[4] http://www.cancerscreening.nhs.uk/prostate/informationpack.html

[5] Moore AL, Dimitropoulou P, Lane A, Powell PH, Greenberg DC, Brown CH et al. Population-based prostate-specific antigen testing in the UK leads to a stage migration of prostate cancer. *BJU Int* 2009; 104(11):1592-1598