

# NATIONAL SCREENING INTEREST GROUP (NSIG)

**Comments to the Screening for Prostate Cancer**  
**Review against programme appraisal criteria**  
**for the UK National Screening Committee (UK NSC)**  
**Dated June 2010**

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**Important Note:** Members of the NSIG are not NHS employees and as such the information, conclusions and recommendations provided in this paper does not necessarily reflect the Plymouth Hospitals NHS Trust's position on national screening for prostate cancer.

23<sup>rd</sup> August 2010

## Summary

The findings, conclusions and recommendations of this paper, dated 23<sup>rd</sup> August 2010, have been provided by the National Screening Interest Group (NSIG), who's membership comprises interested members of the Derriford (Plymouth) Prostate Support Group (PSG).

The main conclusion of this paper is that the number of men's lives that could be saved by national screening for prostate cancer far outweigh the number of complications that could occur as a result of overtreatment. In other words, screening does more "good" than "harm".

A summary of the findings in this paper as well as its conclusions and recommendations are:

### Lives Saved by Screening

The NSIG believes that national screening for prostate cancer will undoubtedly save lives considering the findings of a recent trial carried out in Sweden, a trial in Austria, screening in the USA and recent research carried out in the UK. When considered collectively these trials and research indicate that deaths could be reduced by as much as 50% from national screening.

Further evidence that national screening would save lives is the halting of the rapid rise in prostate cancer mortality when the PSA test was introduced in the late 80s and the 35% reduction in deaths from breast cancer when screening was introduced in 1989.

The European Randomised Study of Screening for Prostate Cancer) shows that screening will save lives, however a 20% reduction appears understated.

Furthermore, a form of prostate cancer screening already takes place in the UK for the "Privileged and Fortunate" which is probably another reason why mortality rates are not increasing as rapidly as they did twenty years ago. Interestingly, men at greatest risk of being diagnosed with prostate cancer at an advanced incurable stage are the "Ignorant and Unfortunate" who happen to be mainly "blue collar" workers.

### More Harm than Good

Taking a "top down" approach using factual prostate cancer statistics for diagnosis and deaths has shown that for every man that dies of prostate cancer only one man could experience complications from radical treatment.

Also, comparing UK statistics with those of the USA shows that the impact of more men being diagnosed with prostate cancer as a consequence of national screening will not be significant.

Therefore, this begs the question: "how many men suffering complications from radical treatment is one man's life worth? It is this fundamental question that needs to be answered in order to determine whether prostate cancer screening does more "harm" than "good".

### Treatment Complications

The NSIG believes there is insufficient sound evidence to accurately quantify radical treatment complications, their severity and duration. Even so, there are several factors that could be used to help determine radical treatment complications for each man diagnosed with prostate cancer. For example:

- Stage at which his prostate cancer is diagnosed
- His age
- His health
- His life expectancy

Other important factors are:

- The type of procedure used
- The health professional's expertise and skill in carrying out the treatment procedure

This said, interim results from ProtecT (**P**rostate **t**esting for **c**ancer and **T**reatment) trial may help provide some useful information on treatment complications.

Even if it was possible to quantify all this information there is a very important question that needs to be answered and that is "how many potentially aggressive life threatening prostate

cancers would be eradicated through radical treatment? The answer to this question is fundamental because without it would it be impossible to accurately determine the number of overtreatments that could occur with, or without, screening.

### Diagnostic Tests

The NSIG agrees that the PSA test when used in isolation can be unreliable in diagnosing prostate cancer. However, when combined with other tests such as a Digital Rectum Examination (DRE) and a patient's "Risk Factor Assessment" the PSA test can be a powerful indicator of prostate cancer as evidenced by a recent trial carried out in Sweden, a trial in Austria and screening in the USA and how the test helped halt the rapid rise in prostate cancer mortality when introduced in the late 80s.

Since the PSA test became available in 1986 (24 years ago) there has not been any other test developed to replace it. Therefore, the probability of a test that is simple, easy to use and cost effective becoming available in the foreseeable future is highly unlikely, hence the reason why the use of PSA testing needs to continue.

### Support for Screening

From the 25<sup>th</sup> March 2010 Public Debate to answer the question "Should national Screening be introduced for Prostate Cancer?" and the Great PSA Debate on 10<sup>th</sup> November 2009, it is evident that the majority of men who have/have had prostate cancer, as well as their relatives and friends, are in favour of national screening for prostate cancer.

It is also evident that the party line for health professionals in the NHS is not to screen for prostate cancer. As a consequence, very few health professionals openly support screening. However, in the private sector, more health professionals are outspoken about their support for screening.

### Conclusions

Based on the findings in this paper, the conclusion by the UKNSC that 'harms from prostate cancer screening using PSA are currently likely to outweigh the benefits and as a consequence screening for prostate cancer cannot be justified' has been proven wrong.

The conclusions from this paper are:

1. National Population Screening for Prostate Cancer will provide more "good" than "harm" as evidenced by the findings in this paper
2. National Population Screening for Prostate Cancer will significantly reduce the number of deaths from the disease
3. National Population Screening for Prostate Cancer will significantly increase life expectancy of men treated for the disease
4. National Population Screening for Prostate Cancer will significantly reduce the number of complications caused by radical treatment
5. National Population Screening for Prostate Cancer will not significantly increase the number of prostate cancer cases diagnosed
6. A form of prostate cancer screening already takes place in the UK for the "Privileged and Fortunate" group of men
7. National Population Screening for Prostate Cancer will ensure that all men reaching, and/or in, the "at Risk" age group will be invited to make an informed choice on whether to proceed with screening tests
8. Men who decide to proceed with screening tests could benefit by having cancer diagnosed at a very early stage
9. Watchful waiting and active surveillance will reduce the need for radical treatment in most men until factors indicate a change that requires intervention
10. When prostate cancer is diagnosed at a very early stage there are more treatment choices that have less inherent complications

11. Technology is advancing rapidly to increase treatment options and reduce treatment complications
12. Although a PSA test cannot detect cancer and/or determine if a cancer is slow growing or aggressive when used in isolation, its result can be combined with known risk factors such as age, ethnicity, family history, height, BMI, diet and other contributing factors, as well as the findings from a Digital Rectum Examination (DRE), to determine a patient's risk factor

### Recommendations

The recommendations, based on the findings in this paper, are as follows.

1. Men aged 50 years (45 years if at high risk), and then each year thereafter, to be invited by the DoH (or appropriate government body) to attend a specific clinic on a specific time and date to complete a risk assessment questionnaire, take a PSA blood test and have a Digital Rectum Examination (DRE) after having made an informed choice to proceed with the screening tests.
2. A Breast Cancer benchmark should be produced by the UKNSC to assess whether prostate cancer meets screening programme appraisal criteria based on the fact that both cancers are similar in terms of potential harm through overtreatment yet one has national screening and one has not and one has seen mortality reduced and one has not.
3. Publish interim findings from the **Prostate testing for cancer and Treatment ( ProtecT)** study to help provide some factual information on treatment complications.
4. The UKNSC appraisal criteria should include quantifiable data measures as well as subjective measures to determine whether the need for screening is justified or not.
5. The value of one man's life in terms of the number of men with complications resulting from overtreatment should be determined as this is essential in assessing an acceptable balance between "Harm" and "Good".

## 1. Introduction

This paper, dated August 2010, have been provided by the National Screening Interest Group (NSIG), who's membership comprises interested members of the Derriford (Plymouth) Prostate Support Group (PSG), for the purpose of providing comments and feedback into the prostate cancer screening expert review consultation ending 21<sup>st</sup> September 2010.

Having taken note of the conclusions contained in the Screening for Prostate Cancer Review against programme appraisal criteria for the UK National Screening Committee (UK NSC), dated June 2010 (see Appendix A), the NSIG has used the information provided in the following sections to explain why it believes these conclusions are incorrect.

- Lives Saved by Screening
- More Harm than Good
- Treatment Complications
- Diagnostic Tests
- Support for Screening

Sections providing conclusions and recommendations are also provided as is Appendix A: Conclusions from the Screening for Prostate Cancer Review against programme appraisal criteria for the UK National Screening Committee (UK NSC), dated June 2010.

## 2. Lives Saved by National Screening

Based on the information provided in this section, a 20% reduction in the number deaths resulting from screening, as claimed in the European Randomised Study of Screening for Prostate Cancer, appears understated when considering the findings from research carried out in the UK, a recent trial carried out in Sweden, a trial in Austria and screening in the USA.

By using common sense and logic there is no doubt that national population screening for prostate cancer will save lives based on the following.

- The earlier prostate cancer is diagnosed the greater the possibility of a cure
- The earlier prostate cancer is diagnosed the greater chance it has of being at a localised stage within the prostate gland
- Localised prostate cancer has the greater the number of treatment options that can be used to cure the disease
- The vast majority of prostate cancers would be diagnosed at a localised curable stage by the introduction of national screening

Based on the findings and information provided in this section a reduction in mortality from prostate cancer is expected to be greater than 50% from national screening in the UK.

### **UK Research**

Scientists at Cancer Research UK have shown that screening for prostate cancer using the prostate specific antigen (PSA) blood test would lead to a substantial number of tumours diagnosed at an earlier and more treatable stage. However, there would be likely cases of overdiagnosed prostate cancer according to a study published in the British Journal of Cancer on the 1<sup>st</sup> April 2009.

The researchers studied 43,842 healthy men given PSA testing as part of the **Prostate testing for cancer and Treatment ( ProtecT)** study to calculate the number of advanced stage prostate cancers picked up as a result of the testing. They also worked out the length of time during which prostate tumours do not produce symptoms but are detectable by a screening test - the Mean Sojourn Time (MST).

The MST test is a method of calculating 'overdiagnosis' and was used to estimate the probability of a diagnosis of prostate cancer which would not have caused symptoms during the patient's lifetime if screening had not taken place. The MST did not increase with age in the age groups 50-59 and 60-69 which showed an MST of 11.3 and 12.6 years respectively.

Some 1,544 men aged 50-69 were diagnosed with prostate cancer through the PSA testing. Overdiagnosis was estimated at one in 10 in the 50-59 age group and increased to three in 10, (31 per cent) in the 60-69 age group. However, after adjusting for overdiagnosis, two-yearly PSA testing might still result in a reduction in advanced stage prostate cancer of up to 54 per cent.

More than 85 per cent of prostate cancer cases could be detected by a two-year inter-screening interval. This was predicted to reduce advanced stage prostate cancer in men 65-69 by 37 percent and men aged 50-54 by 63 per cent. With over-diagnosed cases removed the estimated reductions were nine and 54 per cent respectively.

Study author, Dr Nora Pashayan, a Cancer Research UK scientist at the University of Cambridge, said: "Our results indicate a benefit of screening to reduce the risk of advanced stage prostate cancer. However, this is limited by overdiagnosis. Any screening strategy should take account of the potential benefits and harms of screening. A valuable target for future research would be to estimate the benefit of screening at different ages."

**Source:** Cancer Research UK Press Release, 1<sup>st</sup> April 2009

### **Swedish Trial**

Researchers from the University of Gothenburg, Sweden, conducted a trial involving 20,000 men, aged between 50 and 65 years old, who were divided equally into a group that was offered prostate screening and another group that was not. The results of the trial, which began December 1994 and ended December 2008, showed that prostate cancer screening saves lives and may cut prostate cancer mortality by nearly a half over 14 years concluding that prostate cancer screening compared favourably with screening for other cancers.

The study also found that for every prostate cancer death prevented, 293 men were invited to participate in the screening programme of which 12 were diagnosed with the disease. However, the 12 men who were diagnosed didn't necessarily receive aggressive treatment as some were placed on active surveillance as a way to deal with a cancer whose diagnosis characteristics made it less likely to be life threatening.

An observation made by the authors of the study is that the longer men who participate in a screening programme are followed, the more cancers are eventually diagnosed, lowering the number needed to be screened to save a life. Because of a 10-year time lag before the real benefits of screening begin to appear, it is believed that routine screening for men aged over 70 is considered questionable.

In conclusion, the study proves that in certain circumstances PSA testing and early diagnosis reduces death from prostate cancer.

**Source:** Details extracted from editorial in the Wall Street Journal (1<sup>st</sup> July), Reuters 30<sup>th</sup> June and Medical News Today regarding an article about the trial published in the journal *The Lancet Oncology*.

### **Austrian Trial**

The reduction in deaths through screening can be further evidenced by the trail in Austria, where in 1988 screening started in Tyrol (one of 7 districts in Austria). Since 1988 (over 20 years ago) deaths have reduced by 54% in Tyrol compared with 29% in the rest of Austria. The reduction in the rest of Austria is attributed to "self initiated screening" based on the well publicised success in Tyrol.

**Source:** Tyrol Prostate Cancer Demonstration Project: early detection, treatment, outcome, incidence and mortality. Bartsch et al. *BJU International*. 101, pp 809-816 (April 2008).

### **Screening in the USA**

To further reinforce this 54% reduction in prostate cancer deaths from screening, the UK and USA statistics comparison shown in table 3 below indicates that with national screening, based on the USA statistics, deaths from prostate cancer will reduce by more than 50%.

<b><u>Annual Statistics</u></b>	<b><u>UK</u></b> <b><u>(No Screening)</u></b>	<b><u>USA</u></b> <b><u>(With Screening)</u></b>
<b>Population</b>		
UK Population	61,000,000	
USA Population		308,000,000
<b>Annual Cases Diagnosed</b>	<b>35,000</b>	<b>192,000</b>
Percentage of Population Diagnosed (%)	0.057	0.062
Percentage of Population Difference (%)	0.005	
Additional UK Cases to Match the USA	3,026	
<b>Annual Deaths</b>	<b>10,000</b>	<b>27,000</b>
Deaths versus number Diagnosed (%)	29	14
<b>Estimated UK Deaths with Screening</b>	<b>4,922</b>	
<b>Reduction in UK Deaths with Screening (%)</b>	<b>51</b>	

Source: USA National Cancer Institute Website

**Table 3: Comparison of UK and USA Prostate Cancer Statistics**

As screening in the USA is effectively as a result of widespread private health insurance, the impact of approximately 32 million people who do not have private health insurance needs to be considered. This means that the potential screened population is 276 million (308,000,000 – 32,000,000 = 276 Million). However, men without private health insurance do have access to medical care and if diagnosed with prostate cancer they are included in the 192,000 cases diagnosed.

Also, men diagnosed with prostate cancer who do not have private health insurance are more likely to be diagnosed at an advanced or locally advanced stage. This means they are therefore more likely to die from the disease compared with men diagnosed who have private health insurance. The 27,000 reported deaths also include men with and without private health insurance.

Therefore, the impact of 32 million people who do not have private health insurance has effectively reduced the life saving benefits of screening as illustrated in table 4 that would have been possible if the whole of the population had private health insurance.

### **UK National Screening Calculation**

From using the input data listed below, a simple spreadsheet calculated that the number of deaths from prostate cancer could be reduced from approximately 10,000 deaths each year to around 4,600 deaths, a reduction of 54%.

Also, the increased use of PSA testing and national screening in the USA resulted in 91.1% of men with prostate cancer living more than 5 years compared with only 51.1% in the UK.

Further, since breast cancer screening was introduced in 1989 the annual death rate has reduced by approximately 35%. Similarly, deaths from cervical cancer have decreased dramatically to less than 1,000 deaths a year since screening started in 1967.

Based on the points mentioned above, a reduction in deaths from prostate cancer of 54% through national population screening is considered to be realistic.

The input data listed below was used for the simple spreadsheet calculation.

### **General Input Data Before and After Screening:**

- Men diagnosed with prostate cancer each year in the UK = 35,000
- Deaths from prostate cancer each year in the UK = 10,000
- Percentage of men dying because of localised prostate cancer = 5%
- Percentage of men dying because of locally advanced prostate cancer = 17%
- Percentage of men dying because of advanced prostate cancer = 90%

**Note:** A conservative estimate of 90% has been used for advanced prostate cancer deaths because a number of men will die of other causes.

Input Data Before Screening:

- Percentage of men diagnosed with localised prostate cancer = 43%
- Percentage of men diagnosed with locally advanced prostate cancer = 34%
- Percentage of men diagnosed with advanced prostate cancer = 23%

**Sources:** Prostate Cancer Risk Management Programme: information for primary care; PSA testing in asymptomatic men. NHS Cancer Screening Programmes, 2009” booklet. Cancer Screening Evaluation Unit (DoH) website. PCaSO Prostate Cancer Network Report (Page 3) on a Questionnaire from a survey of 230 members of PCaSO, September 2009

Input Data After Screening:

- Percentage of men diagnosed with localised prostate cancer = 75%
- Percentage of men diagnosed with locally advanced prostate cancer = 18%
- Percentage of men diagnosed with advanced prostate cancer = 7%

**Note:** A conservative estimate of 7% for men diagnosed with advanced prostate cancer has been used because some men will ignore screening appointments.

As mentioned previously, the spreadsheet shown in table 4 below was used to calculate a reduction of 54%.

It is recognised that this reduction in deaths from prostate cancer will not occur immediately as national screening would need to have been in place for a number of years for these benefits to be realised.

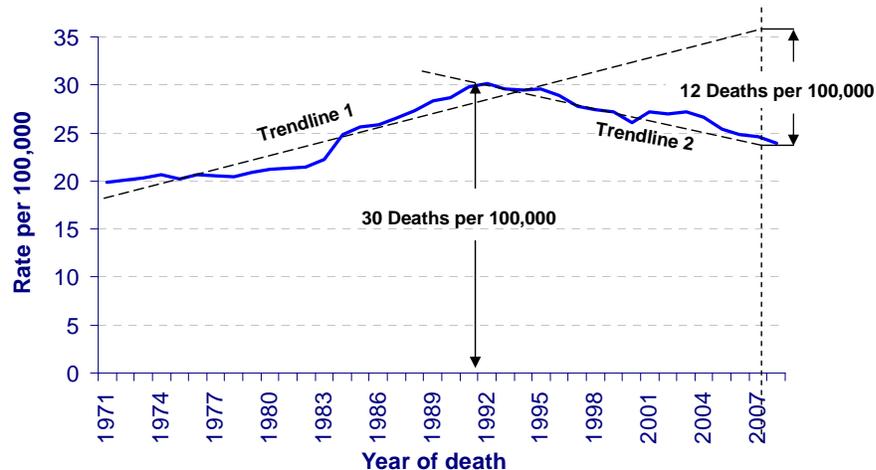
For example, it took approximately 18 years for cervical cancer deaths in women to drop by 50%. Although breast cancer in women started in 1989 (over twenty years ago), deaths have been reduced by approximately 35%. Even so, national screening when implemented would start to save lives immediately.

From these trends it is highly likely that lives saved by screening for cervical and breast cancer will be replicated by screening for prostate cancer. Why should prostate cancer be any different?

<b><u>Annual Statistics</u></b>		<b>(No.)</b>			
<b>Cases Diagnosed</b>		<b>35,000</b>			
<b>Deaths</b>		<b>10,000</b>			
<b><u>Before Screening</u></b>				<b><u>After Screening</u></b>	
<b>Stage at Diagnosis</b>	<b>(%)</b>	<b>(No.)</b>		<b>Stage at Diagnosis</b>	<b>(%) (No.)</b>
Localised	43	15,050		Localised	75 26,250
Locally Advanced	34	11,900		Locally Advanced	18 6,300
Advanced	23	8,050		Advanced	7 2,450
<b>Totals</b>	<b>100</b>	<b>35,000</b>		<b>Totals</b>	<b>100 35,000</b>
<b>Death Rate per Stage</b>	<b>(%)</b>	<b>(No.)</b>		<b>Death Rate per Stage</b>	<b>(%) (No.)</b>
Localised	5	753		Localised	5 1,313
Locally Advanced	17	2,023		Locally Advanced	17 1,071
Advanced	90	7,245		Advanced	90 2,205
<b>Totals</b>		<b>10,021</b>		<b>Totals</b>	<b>4,589</b>
				<b>(%)</b>	<b>(No.)</b>
			<b>Reduction in Deaths</b>	<b>54</b>	<b>5,432</b>

**Table 4: UK Reduction in Prostate Cancer Deaths Spreadsheet Calculation**

Further evidence that national screening would save lives is the halting of the rapid rise in prostate cancer mortality when the PSA test was introduced in the late 80s. From figure 2 below (reproduced from figure 1 in section 2) it can be seen that if the rising mortality trend in continued, deaths would rise from 30 deaths per 100,000 in 1991 to 36 deaths per 100,000 in 2008, an increase of 20% as illustrated by trendline 1.



**Figure 2: Reduction in Mortality caused by introduction of PSA test in the late 80s**

When the impact of PSA testing started to take effect after 1991 mortality decreased to approximately 24 deaths per 100,000 in 2008, a decrease of 20% as illustrated by trendline 2. The true impact of PSA testing was to reduce mortality by 12 deaths per 100,000 a reduction of approximately 33% in just 17 years when compared with 36 deaths per 100,000 as illustrated by trendline 1 if PSA testing did not occur.

Even though there is no “official” screening programme in the UK at present, a form of screening already takes place for the “Privileged and Fortunate”. For Example:

- Those with Health Insurance that covers screening
- Those that have a GP that screen men at risk
- Those that know they are at risk because of family genes
- Health professionals that know the symptoms and risks
- Those that are aware they can have an annual PSA test
- Those that are more generally aware of health matters

These reasons are probably why deaths from prostate cancer are not increasing as rapidly each year as they did twenty years ago, even with men living longer. This means we have an unbalanced playing field comprising the “Privileged and Fortunate” and the “Ignorant and Unfortunate”.

The main cause of imbalance between the two groups is lack of awareness (ignorance) of the symptoms and risks of prostate cancer. Unfortunately, the men most at risk of developing incurable advanced prostate cancer are “blue collar” workers, which seems to indicate a “class” division between the two groups.

Even though it is often quoted that “more men die with prostate cancer than from the disease”, the estimates provided above, combined with the lack of actual data, means that this observation should not be used as justification “not to implement” national screening.

### Section Summary

The NSIG believes that national screening for prostate cancer will undoubtedly saves lives when considering the findings of a recent trial carried out in Sweden, a trial in Austria, screening in the USA and recent research carried out in the UK, which when considered collectively indicate that deaths could be reduced by as much as 50% from national screening.

Further evidence that national screening would save lives is the halting of the rapid rise in prostate cancer mortality when the PSA test was introduced in the late 80s and the 35% reduction in deaths from breast cancer when screening was introduced in 1989.

Although the 20% reduction in the number of deaths resulting from screening (as claimed in the European Randomised Study of Screening for Prostate Cancer) indicates that screening will save lives, it appears understated when considering the findings in this paper.

Furthermore, a form of prostate cancer screening already takes place in the UK for the "Privileged and Fortunate" which is probably another reason why mortality rates are not increasing as rapidly as they did twenty years ago. Interestingly, men at greatest risk of being diagnosed with prostate cancer at an advanced incurable stage are the "Ignorant and Unfortunate" who happen to be mainly "blue collar" workers.

### **3. More Harm than Good**

Compliance with the Hippocratic Oath is being quoted by health professionals as the reason why national screening for prostate cancer cannot be justified. For example, the following extract "To practice and prescribe to the best of my ability for the good of my patients, and to try to avoid harming them" is often quoted because prostate cancer treatments (radical prostatectomy, radiotherapy and brachytherapy) can cause serious complications such as incontinence, erectile dysfunction/impotence and bowel problems when the cancer being treated may not be life threatening.

Even though the Hippocratic Oath makes no reference to saving life, answers to the following questions may help clarify its importance.

1. Does "knowingly" carrying out a radical treatment that can cause "serious complications (harm)" go against the Hippocratic Oath?
2. Is the greatest harm "knowingly" allowing men "at risk" to develop prostate cancer and die from the disease?

The NSIG hopefully believes that the answer to question 1 is "No", the reason being that the overriding purpose of treatment is to save life and/or increase life expectancy.

The NSIG believes that the answer to question 2 must be "Yes", simply because health professionals know that early diagnosis of cancer reduces mortality and yet they do not encourage use of the PSA test and/or support screening to achieve early diagnosis of the disease.

Based on the above it is clear that reference to the Hippocratic Oath as justification for not screening is wrong and unethical, especially as the number of men experiencing complications from treatment is estimated to be the same number as those that die from prostate cancer. In other words, for each man that suffers complications one man dies. Proof of this fact is as follows.

Table 5 below uses the national statistics for prostate cancer diagnosis and deaths to calculate the maximum number of men that could undergo radical treatment for each man that dies from the disease each year.

Even though the 10,000 men in the UK that die each year from prostate cancer are not all from the 35,000 diagnosed each year, the running total over several years of approximately 35,000 diagnosed and 10,000 deaths means that both figures can be considered together for the purpose of this calculation.

Therefore, from table 5 below, it can be seen that for each man that dies from prostate cancer there is a maximum of 2.5 men that could receive radical treatment for the disease ( $35,000 - 10,000 = 25,000$ .  $25,000/10,000 = 2.5$ ).

<b><u>Annual Statistics</u></b>	<b>(No.)</b>
Diagnosed	35,000
Deaths	10,000
Possible Treatments (Diagnosed number less Deaths)	25,000
<b>Maximum Number of Treatment Complications per Death</b>	<b>2.5</b>

**Table 5: Maximum Number of Radical Treatments per Death**

This calculation does not consider the reduction in radical treatment possibilities as a result of the following.

- Watchful waiting
- Active surveillance
- Deaths from other causes

Even though watchful waiting and active surveillance is available to all patients with relatively low PSA levels and/or low Gleason scores, many men who have underlying health problems who may not survive radical treatments are often placed on watchful waiting, active surveillance or given hormone therapy to slow down their cancer growth, especially older men with a reduced life expectancy.

The most significant impact on the number of men who could receive radical treatment is death from other causes. For example, it is believed that some men die from natural causes before radical treatment commences and some men die from the side effects of treatments such as hormone therapy and chemotherapy, the side effect risks being heart attacks, thrombosis, strokes and organ failure. It is also suspected that some men with advanced prostate cancer take their own life when they reach the unbearable final stages of the disease.

As death certificates only record the actual cause of death, the underlying cause of death, being prostate cancer, is not always recorded. These deaths from other causes would significantly reduce the maximum number of men that could undergo radical treatment.

Interestingly, the fact that men with aggressive life threatening prostate cancer often die from other causes means the annual statistic of approximately 10,000 deaths is understated.

From the men that actually undergo radical treatment not all of them will suffer complications. Also, those that do suffer complications the severity of the complication and the time it lasts varies significantly (see section 5).

Taking these factors into consideration it is reasonable to assume that the maximum number of men who could experience complications from radical treatment, for each man that dies of prostate cancer, is approximately one.

Most importantly, this calculation does not consider the number of aggressive “Tiger” cancers that would have been treated successfully from the radical treatment, this being the fundamental reason why Urologists and Oncologists perform these radical treatments. In other words, they perform them to save a man’s life.

However, this calculation is based on statistics reflecting the current situation and therefore does not consider the impact that national screening would have on increasing the number of radical treatments.

The impact of more men being diagnosed with prostate cancer as a consequence of national screening will not be significant as evidenced by comparing the number of men diagnosed with prostate cancer in the UK where there is no “official” screening and the USA where there is screening as a consequence of widespread private health insurance.

For example, the additional number of men diagnosed in the UK as a percentage of the population to match the USA is 0.005%. This represents approximately 3,000 new cases each year through screening (see section 1 above).

Taking all these factors into consideration, it is reasonable to assume that in reality the current situation in the UK without national screening is that for every man that dies of the disease one man will suffer complications. If national screening was to be introduced in the UK, the number of men with complications would be approximately three for every man that dies assuming a 50% reduction in deaths through screening.

### Section Summary

Taking a “top down” approach using factual prostate cancer statistics for diagnosis and deaths has shown that for every man that dies of prostate cancer only one man could experience complications from radical treatment.

Also, comparing UK statistics with those of the USA shows that the impact of more men being diagnosed with prostate cancer as a consequence of national screening will not be significant.

Therefore, these facts beg the question “how many men suffering complications from radical treatment is one man’s life worth? It is this fundamental question that needs to be answered in order to determine whether prostate cancer screening does more “harm” than “good”.

## **4. Treatment Complications**

With regard to complications resulting from unnecessary treatments (over treatment) the figure of 48 men requiring treatment to save one man’s life, as cited in the European Randomised study, appears overstated when the prostate cancer statistics for diagnosis and deaths has shown that for every man that dies of the disease only one man could experience complications from radical treatment as indicated in section 3 above.

Besides taking a “top down” approach using prostate cancer statistics for diagnosis and deaths, the NSIG has also looked at the impact that national screening will have on reducing treatment complications resulting from radical prostatectomy, radiotherapy and brachytherapy, these being the gold standard treatments currently used by the NHS.

For example, it is well accepted that the earlier prostate cancer is diagnosed the higher the probability it has of being contained within the prostate capsule. As early stage localised prostate cancer has the greatest number of treatment options available to eradicate the disease and because the cancer is smaller, less treatment damage is caused to surrounding healthy tissue and organs, resulting in both fewer complications and less severe complications.

The key questions regarding treatment complication are:

1. How many men suffer complications from radical treatment?
2. How severe are these complications from radical treatment?

Answering these questions provides a more realistic measure of “harm” than just relying on 48 men that need to be treated to save one man’s life.

To some extent these questions have been partly answered by the reduction in complications and their severity resulting from early diagnosis as mentioned previously. However, to answer these questions more accurately the complications resulting from radical prostatectomy, radiotherapy and Brachytherapy need to be quantified.

Unfortunately, quantifying the number of complications from these radical treatments is not a simple matter even though there are many studies that have been conducted in a number of countries. However, the following information may be useful.

### Radical Prostatectomy Complications

#### *Erectile Dysfunction/Impotence*

Up to 80% of men experience erection problems after a prostatectomy. The nerves that control a man’s ability to have an erection lie next to the prostate gland. They often are damaged or removed during surgery. Even though nerve sparing surgery can be performed, it carries a risk that not all cancerous cells are removed. In the months and years after surgery, most men who had erection problems after prostatectomy are able to regain their ability to have erections

- 76% of men younger than 60 regain erectile function
- 56% of men age 60 to 65 regain erectile function
- 47% of men older than 65 regain erectile function

Recovery depends on:

- Whether the man was able to have an erection before surgery
- How the surgery affected the nerves that control erections
- How old the man was at the time of surgery

#### *Urinary Incontinence*

Up to half of all men who have a radical prostatectomy develop urinary incontinence ranging from a need to wear urinary incontinence pads to occasional dribbling. Studies show that one year after treatment, between 15% and 50% of men report urinary problems.

The urethra-the tube that carries urine from your bladder-runs through the middle of the doughnut-shaped prostate gland. In order to remove the prostate, the surgeon must cut the urethra and later reconnect it to the bladder. Some men may require treatment for incontinence after prostatectomy if urinary leakage continues longer than 1 year.

#### Radiotherapy Complications

The side effects of radiotherapy include most of those of surgery, but the risks for impotence and incontinence are considerably lower. A 2000 study concluded that adjuvant radiation therapy (given right after surgery) in moderate doses does not increase the risk for long-term urinary incontinence or sexual dysfunction beyond that of surgery alone.

#### *Erectile Dysfunction/Impotence*

In a 2003 meta-analysis, the risk for impotence following radiotherapy was up to 45% with external beam radiotherapy.

#### *Urinary Incontinence*

The risk for incontinence is about 7% to 20%. Patients treated with radiation may experience a painful, but usually temporary, urinary tract inflammation. About 10% to 15% of patients develop a long-term urgent and frequent need to void their bladder.

#### Brachytherapy Complications

#### *Erectile Dysfunction/Impotence*

In a 2003 meta-analysis, the risk for impotence following brachytherapy was up to 25%. However, there are very few studies on brachytherapy that have lasted more than two years, so more research is needed.

#### *Urinary Incontinence*

Brachytherapy carries a lower risk for urinary incontinence than both radical prostatectomy and external beam radiotherapy.

The information on complications from radical prostatectomy, radiotherapy and brachytherapy can be summarised as follows in table 6 below.

<b>Treatment</b>	<b>Erectile Dysfunction/ Impotence Complications</b>	<b>Urinary Incontinence Complications</b>	<b>Bowel Complications</b>
Radical Prostatectomy	< 80%	15 to 50%	Not Known
Radiotherapy	< 45%	7 to 20%	Not Known
Brachytherapy	< 25%	< 20%	Not Known

**Table 6: Treatment Complications (Source: Web MD)**

From table 6, approximately 50% of all radical treatments cause some form of erectile dysfunction/impotence complications with approximately 25% causing urinary incontinence complications. What is not quantified is the severity of these complications.

Like all surgery and treatments, evidence shows that the greater the experience and skill of the health professional carrying out the procedure the lower the risk of complications.

Even though the NSIG accepts that the effects of incontinence, erectile dysfunction/impotence and bowel problems can be debilitating for sufferers, there are many treatments, devices and solutions available to alleviate the suffering. Therefore, with saving life being more important than causing harm the question “how many men suffering complications from radical treatment is one man’s life saved worth? still needs to be answered.

Besides the three gold standard NHS treatments of radical prostatectomy, radiotherapy and brachytherapy, there are other treatments and equipment enhancements (some used by NHS trusts but mainly used in the private health care sector) that claim to be less invasive and cause less complications. These are:

- Da Vinci Robot
- 3D Conformal Radiotherapy
- Intensity Modulated Radiotherapy
- RapidArc
- Proton Beam Therapy (PBT)
- HIFU
- Cryotherapy
- Photo Dynamic Therapy (PDT)

For example, the Da Vinci Robot allows a less skilled surgeon to perform a radical prostatectomy with the same degree of success as a skilled surgeon. RapidArc™ claims to carry out radiotherapy treatments faster and more accurately than traditional external beam radiotherapy, thus minimising complications as well as cost.

Treatments such as High Intensity Focussed Ultrasound (HIFU) and Photo Dynamic Therapy (PDT) are less invasive and therefore result in cause less complications. In addition, the use of Proton Beam Therapy (PBT) is showing promise in the USA for treating prostate cancer.

### Section Summary

The NSIG believes there is insufficient sound evidence to accurately quantify radical treatment complications, their severity and duration. Even so, there are several factors that could be used to help determine radical treatment complications for each man diagnosed with prostate cancer. For example:

- Stage at which his prostate cancer is diagnosed
- His age
- His health
- His life expectancy

Other important factors are:

- The type of procedure used
- The health professional’s expertise and skill in carrying out the treatment procedure

This said, interim results from ProtecT (**P**rostate **t**esting for **c**ancer and **T**reatment) trial may help provide some useful information on treatment complications.

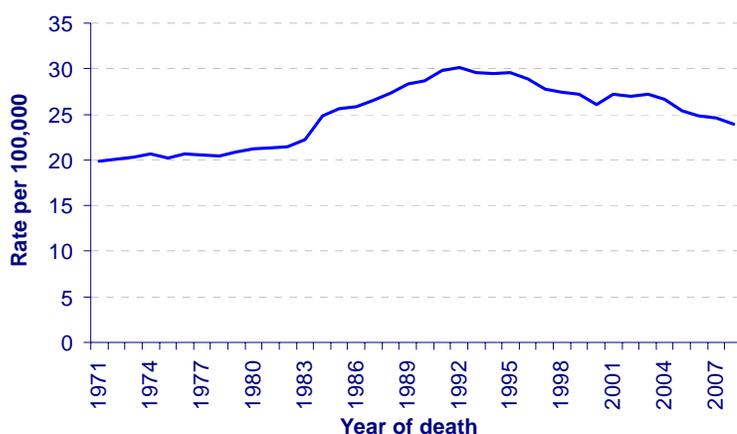
Even if it was possible to quantify all this information there is a very important question that needs to be answered and that is “how many potentially aggressive life threatening prostate cancers would be eradicated through radical treatment? The answer to this question is fundamental because without it would it be impossible to accurately determine the number of overtreatments that could occur with, or without, screening.

## 5. Diagnostic Tests

The age standardised (European) mortality rate for prostate cancer peaked in 1991 and then reduced thereafter as can be seen in figure 2 below. However, the actual death rate has continued to rise.

When the Prostate Specific Antigen (PSA) test became available in the late 80s its widespread use halted the rapid rise in prostate cancer mortality. Even after the Department of Health made the decision in 1997 not to introduce national screening for prostate cancer and in doing so actively discouraged GPs from using the test, the mortality rate did not rise significantly

Since the PSA test became available in 1986 (25 years ago) there has not been any other test developed to replace it. Therefore, the probability of a test that is simple, easy to use and cost effective test becoming available in the foreseeable future is highly unlikely.



**Figure 2:** Age-standardised (European) mortality rates, prostate cancer, UK, 1971-2008

Even though use of the PSA test is clearly responsible for halting the rise in mortality, the NSIG agrees that the PSA test when used in isolation can be unreliable in diagnosing prostate cancer. However, the PSA test can be used in conjunction with other efficient and cost effective tests to help improve prostate cancer diagnosis. For example:

- A Digital Rectum Examination (DRE)
- A simple computer programme using known risk factors such as age, ethnicity, family history, height, BMI, diet and other contributing factors to determine the patient's risk factor

If the PSA, DRE and Risk Factor Assessment when combined indicate high risk further recognised steps can be taken such as:

- Watchful waiting which may require a series of PSA tests to be carried out over a period of time to identify whether a patient's PSA is rising
- Ultrasound scan of the prostate to identify any abnormalities
- Active surveillance which may require a series of PSA tests, ultrasound scans and prostate biopsies to be carried out over a period of time to identify whether a patient's cancer is progressing and potentially becoming more aggressive

Furthermore, other PSA test variants are showing promise at diagnosing prostate cancer.

### PSA Free to Total Ratio

PSA exists in different forms within the systemic circulation, furthermore it has a tendency to form complexes with other molecules. Studies in 1991 revealed that complexed PSA was greater in patients with cancer than in those with Benign Prostatic Hypertrophy (BPH), an enlargement of the prostate gland.

Therefore, the free-to-total ratio had the potential to enhance the performance of PSA testing. It is probably of most use in patients with a PSA level of 1-4 ng/ml and 4-10ng/ml with a normal DRE. Despite the fact that this method appears to be the most promising, it must be noted that the exact ratio to determine further investigation has yet to be established.

#### PSA Velocity (speed)

This test involves measuring the rate of change in PSA values over time. Studies have shown a linear increase in patients with BPH, whereas patients with cancer had an initial linear increase followed by an exponential rise. In a recent European consensus article a PSA velocity of > 0.75ng/ml/yr in a patient with a PSA between 4-10ng/l was deemed significant. Furthermore, the velocity should be calculated over 18 months with three separate values. Significant velocities in patients with PSA values <4ng/ml have yet to be determined.

#### PSA Density

This measurement is obtained by dividing the serum PSA by the volume of the prostate gland. Certain studies have demonstrated that PSA density performed significantly better than PSA in differentiating between patients with and without cancer. However other studies have failed to agree.

**Source:** Bristol Urology Associates

#### Section Summary

The NSIG agrees that the PSA test when used in isolation can be unreliable in diagnosing prostate cancer. However, when combined with other tests such as a Digital Rectum Examination (DRE) and a patient's "Risk Factor Assessment" the PSA test can be a powerful indicator of prostate cancer as evidenced by a recent trial carried out in Sweden, a trial in Austria and screening in the USA and how the test helped halt the rapid rise in prostate cancer mortality when introduced in the late 80s.

Since the PSA test became available in 1986 (24 years ago) there has not been any other test developed to replace it. Therefore, the probability of a test that is simple, easy to use and cost effective becoming available in the foreseeable future is highly unlikely, hence the reason why the use of PSA testing needs to continue.

### **6. Support for Screening**

The following pie charts are from a Report on the 25<sup>th</sup> March 2010 Public Debate to answer the question "Should national Screening be introduced for Prostate Cancer?" sponsored by the Derriford Hospital (Plymouth) Prostate Support Group (PSG) Steering Group.

The vote before (vote 1) and after the debate (vote 2), clearly illustrates how important the need for screening is to men who have and/or had prostate cancer and their family and friends, even after three Derriford Hospital Consultants put forward a more convincing argument not to screen than the argument for screening put forward by one prostate cancer sufferer with no healthy professional support.

#### **Vote 1 and Vote 2 Results From by Men who Have/Have Had Prostate Cancer**

The results of Vote 1 and Vote 2 from by men who have/have had prostate cancer are shown in Chart 1 and Chart 2 respectively below.

At the start of the debate 68% of men who have/have had prostate cancer were a favour of national screening but at the end of the debate this had dropped to 51%. This indicated a 17% movement towards not screening by the end of the debate.

For example, the votes against screening increased by 10% to 26% and the undecided votes increased by 7% to 23%. However, 11 men (36%) changed their vote position by the end of the debate, which is not indicated in the pie charts.

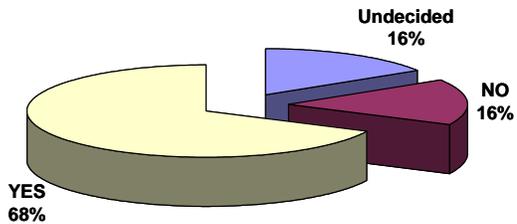


Chart 1: Vote 1 Result

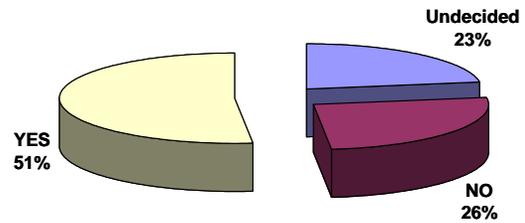


Chart 2: Vote 2 Result

**Vote 1 and Vote 2 Results From Family/Friends of men who Have/Have Had Prostate Cancer**

The results of Vote 1 and Vote 2 from family/friends of men who have/have had prostate cancer are shown in Chart 3 and Chart 4 respectively below.

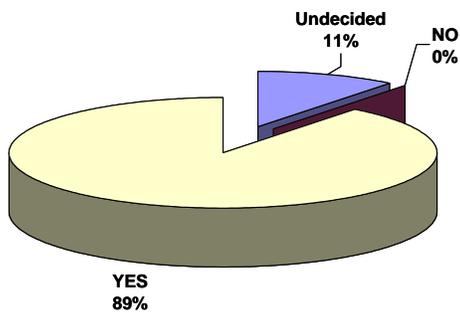


Chart 3: Vote 1 Result

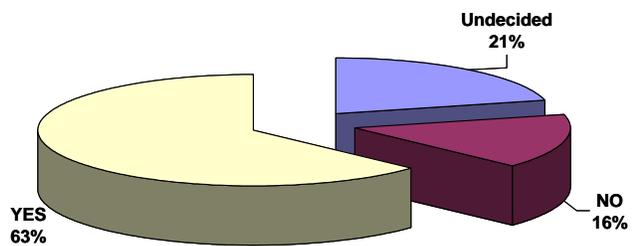


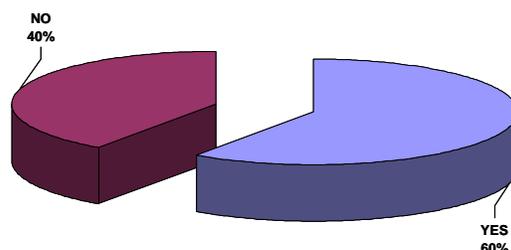
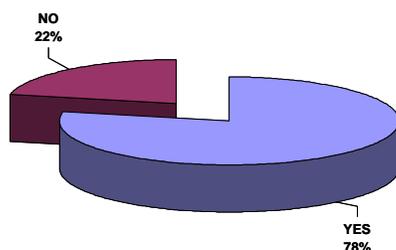
Chart 4: Vote 2 Result

At the start of the debate 89% of family/friends of men who have/have had prostate cancer were a favour of national screening but at the end of the debate this had dropped to 63%. This indicated a 20% movement towards not screening by the end of the debate. For example, the votes against screening increased from no votes to 16% and the undecided votes increased by 10% to 21%. However, 7 family/friends (37%) changed their vote position by the end of the debate, which is not indicated in the pie charts.

On the 10th November 2009 at the Pump Rooms in Leamington Spa, the Prostate Cancer Support Federation, in collaboration with Prostate UK and the Graham Fulford Charitable Trust, held "The Great PSA Debate", to discuss the motion: "Every man at risk of prostate disease (i.e. all men over 50, and those 40 with other risk factors) should be encouraged to check his PSA every year."

To maximize debate findings a detailed questionnaire was completed by 75% of delegates. The following pie charts are from The Great PSA Debate Questionnaire Analysis Report, which provided the findings and conclusions from this questionnaire.

At the start of the debate delegates were also asked to vote whether they support or oppose the need for national screening for prostate cancer. At the end of the debate delegates were asked to vote again whether they support or oppose the need for national screening for prostate cancer. The results of the "before" and "after" vote are shown in the two pie charts left to right.



The conclusion that can be drawn from this voting result is that prior to the debate the majority of respondents felt that national screening was the best solution to identify prostate cancer, whereas concern expressed by health professionals on the expert panel about the failings of diagnostic tools during the debate caused an 18% swing resulting in 40% “against” and 60% “for” national screening. Although the majority of respondents remained in favour of national screening the difference between those “for” and “against” is not significant thus clearly indicating the challenge the UK National Screening Committee (NSC) has in reviewing their position on prostate cancer screening.

### Section Summary

From the 25<sup>th</sup> March 2010 Public Debate to answer the question “Should national Screening be introduced for Prostate Cancer?” and the Great PSA Debate on 10<sup>th</sup> November 2009, it is evident that the majority of men who have/have had prostate cancer, as well as their relatives and friends, are in favour of national screening for prostate cancer.

It is also evident that the party line for health professionals in the NHS is not to screen for prostate cancer. As a consequence, very few health professionals openly support screening. However, in the private sector, more health professionals are outspoken about their support for screening.

## **7. Conclusions**

Based on the findings in this paper, the conclusion by the UKNSC that harms from prostate cancer screening using PSA are currently likely to outweigh the benefits and as a consequence screening for prostate cancer cannot be justified, has been proven wrong.

The conclusions from this paper are as follows.

1. National Population Screening for Prostate Cancer will provide more “good” than “harm” as evidenced by the findings in this paper
2. National Population Screening for Prostate Cancer will significantly reduce the number of deaths from the disease
3. National Population Screening for Prostate Cancer will significantly increase life expectancy of men treated for the disease
4. National Population Screening for Prostate Cancer will significantly reduce the number of complications caused by radical treatment
5. National Population Screening for Prostate Cancer will not significantly increase the number of prostate cancer cases diagnosed
6. A form of prostate cancer screening already takes place in the UK for the “Privileged and Fortunate” group of men
7. National Population Screening for Prostate Cancer will ensure that all men reaching, and/or in, the “at Risk” age group will be invited to make an informed choice on whether to proceed with screening tests
8. Men who decide to proceed with screening tests could benefit by having cancer diagnosed at a very early stage
9. Watchful waiting and active surveillance will reduce the need for treatment in most men until factors indicate a change that requires intervention
10. When prostate cancer is diagnosed at a very early stage there are more treatment choices that have less inherent complications
11. Technology is advancing rapidly to increase treatment options and reduce treatment complications
12. Although a PSA test cannot detect cancer and/or determine if a cancer is slow growing or aggressive when used in isolation, its result can be combined with known risk factors such as age, ethnicity, family history, height, BMI, diet and other contributing factors, as well as the findings from a Digital Rectum Examination (DRE), to determine a patient’s risk factor

## Recommendations

The recommendations, based on the findings in this paper, are as follows.

1. Men aged 50 years (45 years if at high risk), and then each year thereafter, to be invited by the DoH (or appropriate government body) to attend a specific clinic on a specific time and date to complete a risk assessment questionnaire, take a PSA blood test and have a Digital Rectum Examination (DRE) after having made an informed choice to proceed with the screening tests
2. A Breast Cancer benchmark should be produced by the UKNSC to assess whether prostate cancer meets screening programme appraisal criteria based on the fact that both cancers are similar in terms of potential harm through overtreatment yet one has national screening and one has not and one has seen mortality reduced and one has not
3. Publish interim findings from the **Prostate testing for cancer and Treatment (ProtecT)** study to help provide some factual information on treatment complications
4. The UKNSC appraisal criteria with regard to “Good (benefits)” and “Harm” should be quantified instead of being a subjective measure to determine whether the need for screening is justified or not
5. The value of one man’s life in terms of the number of men with treatment complications should be determined as this is essential in assessing an acceptable balance between “Harm” and “Good”

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## Appendix A

### **Screening for Prostate Cancer Review against programme appraisal criteria for the UK National Screening Committee (UK NSC), dated June 2010**

#### 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 identify 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.