

**The UK Genetic Prostate Cancer Study  
UKGPC Study Protocol**

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## 1 BACKGROUND AND INTRODUCTION

PrCa (PrCa) is a significant public health problem. It is the most common non-cutaneous tumour in men in the USA and will be diagnosed in almost one-fifth of US men during their lifetime (Ferlay et al., 2010). In the European Union, approximately 328,000 men are diagnosed annually with PrCa, with the incidence having tripled in the last 40 years (Horwich et al., 2013). In the UK, there are approximately 40,000 new cases per annum and it accounts for 10,721 cancer deaths. The incidence is increasing with a lifetime risk of 1 in 9 in the United Kingdom (Cancer Research UK Cancer Stats, 2010).

There is substantial worldwide variation in disease incidence; the disease is commoner in the Western countries than in the Far East and developing world (Marugame et al., 2006). Multiple aetiologies have been proposed to contribute to the development of PrCa. However, there is strong evidence that inherited genetic factors are important and exhibit significant familial aggregation in some men, particularly when affected at a young age (Woolf et al., 1960; Steinberg et al., 2000; Singh, 2000; Edwards et al., 2003, Edwards & Eeles, 2004).

A segregation analysis by Carter et al. (1992) and later by Paiss (2002) suggested an autosomal dominant gene could account for approximately 43% of PrCa patients diagnosed before age 55 and 9% of cases diagnosed up to age 85 (Simard et al., 2003). There is evidence for the familial aggregation of PrCa. In 1960, Woolf studied the first degree relatives of PrCa cases in the Utah Church of Jesus Christ of Latter Day Saints' population in the USA. By studying death certificates, and comparing them with age-matched controls, he found that first degree relatives of cases had a threefold increased risk of PrCa. Results from other studies have suggested an increased RR of prostate cancer in close relatives of PrCa cases of up to 18-fold, depending upon age of the case and degree of familial clustering. If familial clustering is due to inherited factors, then it would be expected that it would occur more commonly in association with young age at onset of the disease. Cannon (1982) has found that as the age of the proband decreases, the risk of first degree relatives who are <65 increases and Meikle (1985) has also shown that the risk to relatives of cases is higher at younger ages. The dramatic rise in the Relative Risk (RR) as the degree of clustering increases in a PrCa cluster (an increase in the number of cases and a decrease in the average age of onset of cases in a cluster), is too great to be explained by non-genetic factors such as environment alone. PrCa RR rises dramatically the younger the age of the proband, as the number of cases in a cluster increases, and with a combination of these factors. Three segregation analyses (analyses to determine the genetic model) have suggested the presence of at least one high-risk gene of a frequency between 0.3 and 1.0%. This confers a life time risk of 63-88% of developing PrCa, the population risk being 2% by 74 years and just under 10% by 85 years (reviewed in Edwards & Eeles, 2004). Two cohort studies (Goldgar et al., 1994; Gronberg et al., 1997) estimated the RR of PrCa in first-degree relatives to be 2.2. This familial risk is greater in families where the PrCa cases are younger, being more than 4-fold for close relatives of cases diagnosed below age 60. Meta-analysis of the current literature on risk of PrCa among men with a positive family history indicates a RR of 1.8-2.1 and 2.9-fold increased risk respectively, depending on whether the affected relative was a second-degree relative, the father or a brother and higher risks have been shown for men with 2 or more affected relatives. This observed increased risk is too great to be explained by non-genetic factors alone (Carter et al., 1992; Bruner et al., 2003). Analyses based on the Nordic twin registries have also found higher risks in monozygotic compared to dizygotic twins, supporting the hypothesis that much of this familial aggregation is due to genetic factors (42%) rather than shared lifestyle factors (Lichtenstein et al., 2000).

Molecular approaches to the understanding of neoplasia have revealed that multiple genetic alterations are involved in the development of the malignant phenotype (Weinberg, 1989). Often the changes that occur in the genes in cancer cells in sporadic cancers are the same as those that occur in cancers due to an inherited predisposition. The only difference between sporadic and inherited forms of the same cancer type is that those cancers occurring due to an inherited predisposition involve an initiating abnormal genetic event in the germline. Cancers that are due to an inherited disposition therefore tend to occur at younger ages than the sporadic forms of the same cancer.

Although several candidate genes have been reported that may predispose to PrCa, the evidence from linkage analysis and cohort studies is controversial. However, there is a recognised association of breast cancer with PrCa in families (Anderson et al., 1992; Tulinius et al., 1992; Thiessen et al., 1974). Male relatives in breast cancer families in Iceland have a 2-3-fold risk of the disease (Sigurdsson et al., 1997). The breast cancer predisposition genes, breast cancer 1 and breast cancer 2 (*BRCA1* and *BRCA2*) have been reported to increase the risk of PrCa in male carriers of these genes by three-fold and seven-fold respectively (Ford et al., 1994; BCLC, 1999). The results from the Breast Cancer Linkage Consortium (BCLC) showed a RR of 4.65 (95%CI 3.48-6.22) of PrCa in male *BRCA2* mutation carriers and 1.07 (0.75-1.54) in *BRCA1* carriers (with a RR of 1.82 for men under 65 years old) (Thompson et al., 2001; 2002). A recent large study screening almost 2000 men with prostate cancer reported that about 1.2% of young onset cases (<65 years) unselected for family history carried a deleterious mutation in *BRCA2* giving an increased risk of 8.6-fold in men  $\leq$  65 years (Kote-Jarai et al., 2011). The relative risk of PrCa in young *BRCA1* mutation carriers has been more contentious, but a recent study by our team has substantiated the previous BCLC data which show that *BRCA1* mutation carriers also have an increased risk of PrCa up to age 65 years of about 3.8-fold (Leongamornlert et al., 2012).

Deleterious germline mutations in both the *BRCA1* and *BRCA2* genes have been associated with more aggressive disease and poor clinical outcomes, which poses particular issues regarding the management of these patients (Tryggvadottir et al., 2007; Gallagher et al., 2010; Thorne et al., 2011; Castro et al., 2013). Unpublished data (Castro et al., 2013) suggest that PrCa occurring in *BRCA2* mutation carriers has a poorer prognosis after radiotherapy, which may alter our treatment recommendations for this cohort. This illustrates that germline genetic variants can have important prognostic implications for patients with PrCa and need further evaluation.

Although mutations in the *BRCA1/2* genes are moderate-to-high risk PrCa susceptibility alleles, these only account for a very small proportion of the disease at younger ages ( $\leq$ 60 years). There are therefore highly likely to be other genes left to be discovered which may follow several possible models of inheritance and penetrance. The search for genetic alterations responsible for familial disease initially involved linkage analysis which is a powerful tool to search for disease-predisposing genes. It has already been used successfully to find the genetic causes of several of the common cancers, but PrCa has not so far revealed a definitive genetic locus by this technique (over 100 papers reviewed in Edwards & Eeles 2004). This is thought to be due to genetic heterogeneity (several genes are responsible, which are different in different familial clusters). The genetic alterations may also be of lower penetrance i.e. they could be quite common, but confer moderate risks to the individual. Such alterations could account for a substantial proportion of the disease (over 80%) and only still cause single cases at any age or small clusters, which is what is observed. In an effort to identify these alterations Genome-wide association studies (GWAS) were performed, which have now identified over 70 susceptibility loci associated with PrCa (Goh et al., 2011; Al Olama et al., 2011; Eeles et al., 2013). Their clinical utility still undetermined and efforts are currently underway to define this further. Individually, these loci contribute at most a modest increase in PrCa risk, but when these are combined, they could explain approximately a third of the PrCa familial risk (Eeles et al., 2013). Further discovery to explain the missing heritability genes and a better understanding of its functional aspects are needed to help us ascertain the aetiology of prostate cancer.

Currently, the aetiology of PrCa remains very poorly understood, with few established risk factors. The large variations in disease incidence between countries, together with migrant studies, indicate that lifestyle and/or environmental factors are important determinants of PrCa. However, although many environmental factors have been suggested to be associated with PrCa (see below) the results between studies are conflicting. On the other hand as detailed above, a family history of PrCa and some genetic variants have been established as risk factors. The following lifestyle factors have been suggested to contribute to PrCa risk.

**Sexual activity:** Previous studies have suggested that PrCa risk may be associated with a large number of sexual partners, sexually transmitted diseases, early age at first intercourse and frequent intercourse (Key, 1995; Ewings et al., 1996; Hayes et al., 2000). However, few studies have collected a measure of total sexual activity including lifetime histories of sexual intercourse

and masturbation, which we have done. Previous studies are therefore difficult to interpret and compare. Although most factors in sexual exposure are thought to be positively hormone-related, there are several studies suggesting negative associations with PrCa risk: for example increasing age at first intercourse/masturbation (Hayes et al., 2000; Rosenblatt et al., 2001).

More interestingly, overall sexual exposure (intercourse and masturbation), as assessed by ejaculation frequency (EF), showed that high EF conferred decreased risk (Leitzmann et al. 2004). A protective effect, but limited to ejaculations experienced in early adult life, was also found by Giles et al. (2003). More recently, Dimitropoulou et al. (2010) published that frequent overall sexual activity in younger life (20s) increased the disease risk. However, it appeared to be protective against the disease when older (50s). Alone, frequent masturbation activity was a marker for increased risk in the 20s and 30s but appeared to be associated with a decreased risk in the 50s, while intercourse activity alone was not associated with the disease. These findings imply potential different mechanisms, which need further evaluation.

**Radiation exposure:** Early studies (Rooney et al., 1993; Atkinson et al., 1994) have shown associations between radiation exposure and PrCa. Myles et al. (2008) showed that exposure of the prostate gland to diagnostic radiological procedures may be associated with increased cancer risk. This effect seems to be modified by a positive family history of cancer suggesting that genetic factors may play a role in this risk association. However, another study found conflicting results with no significant association between PrCa mortality with radiation dose (Atkinson et al., 2007).

**Sunlight exposure:** Vitamin D is known to be a negative cell cycle regulator. PSA levels in advanced PrCa patients have been shown to drop after treatment with high-dose vitamin D (Beer & Myrthue, 2004). Solar UV-B radiation, acting through vitamin D production, has been identified as a possible protective factor for the disease (Bodiwala et al., 2003; Grant, 2004). However, a recent systematic review did not find any association between serum vitamin D levels and PrCa risk (Gandini et al., 2011).

**Body shape and BMI:** Anthropometric measurements such as body size, obesity and height, have been shown to be positively associated with PrCa in many studies. Meta analysis has shown that height, rather than weight, has a more consistent relationship to PrCa (MacInnis et al., 2006). Results on body mass index (BMI) show greater variation across studies, most likely due to different case/control inclusion criteria between the studies and possibly because the index itself fails to reflect the distribution or composition of body fat and lean body mass. Schuurman et al. (2000) found an association with PrCa and high body mass index at younger ages. Giovannucci et al. (1997), however, examined a US cohort of health professionals showing the opposite association. However, a well-conducted meta-analysis has shown a positive relationship between BMI and death from PrCa, suggesting obesity may play a role in PrCa progression (Hsing et al., 2007). Different distributions of excess weight may be one explanation for this disparity as one suggested mechanism is through an effect on hormonal profile and different body shapes are known to associate with varying hormonal patterns.

**Scalp hair recession:** Baldness is thought to be a marker of androgen production and activity, possibly with an important genetic aetiology (Sinclair, 1998). The pattern of hair loss is associated with number of androgen receptors and 5 $\alpha$ -reductase activity. Severity and onset of baldness by age 40 are associated with PrCa (Denmark-Wahnefried et al., 2000; Giles et al., 2002).

**Diet:** A number of dietary components have been suggested to be involved in PrCa aetiology. For example, it has been suggested that total energy intake, saturated animal fats (perhaps mediated through IGF-I) and high general fat consumption are positively associated with PrCa (Kristal et al., 2002; Hsieh et al., 2003; Rodriguez et al., 2003; Grant, 2004; Lopathananon et al., 2010) although some case-control studies have shown no association (Key et al., 1997; Platz, 2002). PrCa has been specifically associated with high dairy consumption, perhaps mediated through calcium levels (Chan et al., 2001).

For specific foods, a number of significant dose-response relationships have been suggested. In such studies, although there is adjustment for confounding factors, confounding by other dietary habits may still occur. For example, Laaksonen et al. (2004), assessing the association of fatty acid composition and PrCa, indicated that dietary linoleic acid intake is inversely associated with PrCa; however the effect may partly be attributed to nutrients closely associated with vegetable fats.

A case-control study nested within the Health Professionals Follow-up Study (Wu et al., 2004), found that for younger men (<65 yrs) beta-carotene may be protective against prostate carcinogenesis. Other risk-reducing micronutrients include vitamin E (Huang, 2003) and selenium (Bodiwala et al., 2003). Selenium is of particular interest following a randomised trial by Clark et al., which suggested that it may exert a protective role in PrCa, although its effectiveness in younger men is unknown. (Clark et al., 1996; 1997). Giovannucci et al. (1998; 2002) reported a decreased PrCa risk with lycopene intake. Regarding other foods, there is still insufficient evidence of a protective effect of vegetables (Kolonel et al., 2000) or a harmful effect of alcohol in PrCa.

There is therefore considerable uncertainty about both the genetic and environmental causes of PrCa, and there may also be interactions between these factors.

These issues will therefore require several approaches; (i) the study of PrCa families and young onset PrCa cases, (ii) studies of large series of PrCa cases and (iii) the interaction of genetic factors and environment and (iv) the interaction of genetic factors and disease behaviour and treatment outcome, hence this study.

Markers are available through the Human Genome Mapping/HapMap Projects (The International HapMap Consortium, 2005) to enable a search for linkage throughout the human genome. Since the Human Genome Project has been completed, the genetic sequences of a substantial part of the coded genome are known, but which of these are susceptibility genes to PrCa is unknown. Possible sites of a tumour suppressor gene can be identified from sites of chromosomal loss in sporadic tumours. Such loss can be seen cytogenetically or on Southern analysis by loss of heterozygosity. Potential sites of a PrCa tumour suppressor gene indicated by cytogenetic studies include chromosomes 2, 5, Y (Brothman, 1990). The most favoured candidates from loss of heterozygosity studies are 10q and 16q because the highest percentage of loss (30% of tumours) is in these regions (Carter, 1990). Tumour studies are therefore needed. Since the inception of this protocol in 1992, several areas of linkage and candidate genes have been suggested, however, the genetic causes of many of the cases of PrCa and PrCa clusters which may have a genetic predisposition are unknown, hence the collection of further samples and continuation of this study until 2017. (Literature reviewed in Goh et al., 2011).

## **1.1 HISTORY OF THE UKGPCS AND RATIONALE FOR CONTINUATION AND A NEW PROTOCOL**

At the inception of this protocol in 1992, the initial remit was to collect -blood and tumour (both fresh and paraffin embedded samples) from PrCa patients (i) diagnosed at any age from one clinic at The Royal Marsden Hospital (ii) diagnosed at < 55 and then through a protocol amendment, subsequently  $\leq$  60 years, from collaborators throughout the UK (iii) from familial clusters with either two cases where one is <65 years or three or more cases at any age. All cases were consented through one centre (The Institute of Cancer Research/ Royal Marsden NHS Trust). The remit was to look for PrCa genes and assess the RR of PrCa to first degree relatives.

In 1994 the protocol was revised in light of the new MRC guidelines and in 2005, the protocol was re-written to incorporate the new forms that were created (COREC). The study was extended to 2012 to recruit further cases. We started to collect environmental data to correlate with genetic data for gene/environment interactions. We contributed anonymous data from the UKGPCS to international datasets and performed meta analyses (Eeles et al., 2008; Eeles et al., 2009; Amin Al Olama et al., 2009; Lophatananon et al., 2010; Elliott et al., 2010; Al Olama et al., 2011; Lose et

al., 2011; Kote-Jarai et al., 2011; Rahman et al., 2011; Schumacher et al., 2011; Batra et al., 2011; Eeles et al., 2013 ) In 2011 we extended the study to collect samples until the end of 2017, and increased the number of samples as a greater power was required to look for rare genetic variants.

This new protocol has been revised because

- We currently have over 180 NCRN sites that are referring patients to our study. We would like to change the recruitment process so that each site would consent eligible patients and collect samples. This will ensure that a full set of data for all new patients are received and also improve clinical data and epidemiological data collection. We had numerous requests from sites who have asked for the study be localised, giving them control on consenting patients and collecting samples. This will increase the consent rate at recruiting sites.
- We would like to be able to collect saliva samples as it is less invasive for patients.
- We would also like to collect urine samples on newly diagnosed patients prior to treatment to look for new biomarkers.

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## **2 AIMS AND OBJECTIVES**

### **2.1 Aims**

The aims are:

- to find genes which predispose to PrCa
- to determine if genes which predispose to PrCa are associated with disease and treatment parameters and tumour molecular changes
- to find biological markers associated with PrCa, genetic predisposition and disease behaviour
- to determine if genes which predispose to PrCa are associated with environmental factors
- to estimate the percentage of PrCa patients who have a positive family history of the disease
- to estimate the relative risk of developing PrCa in a currently unaffected member of a PrCa family
- to ascertain whether relatives of PrCa patients are at increased risk of developing cancers other than PrCa

Objectives to achieve the aims:

- To build up a large blood/saliva, urine and tumour (both fresh and preserved) bank and clinical database from patients with PrCa to: (i) identify PrCa predisposition gene(s); (ii) determine the prevalence and penetrance of PrCa predisposition genes in PrCa patients; (iii) correlate changes in PrCa predisposition gene(s) with disease and treatment parameters by matching with clinical data from clinical databases already held as part of the medical record on these patients (iv) correlate changes in PrCa predisposition gene(s) with environmental factors collected by questionnaire from these patients
- To use the blood/saliva, urine and tumour bank for marker studies (DNA, RNA, serum, plasma and protein and other molecules) to define the role of these markers in disease prediction and progression
- To develop microarrays from PrCas to determine their genetic profile and correlate this with PrCa genetic predisposition genes.
- To collect tissue from other unaffected and affected members of the family in cases where a genetic alteration is found, in order to ascertain whether this alteration is associated with disease risk.
- To collect tissue samples from unaffected family members who show an interest in taking part in the study.

### **2.2 End Points**

#### **2.2.1 Primary endpoint**

- To identify PrCa predisposition genes

#### **2.2.2 Secondary endpoints**

- To determine if genes which predispose to PrCa are associated with disease and treatment parameters
- To determine if genes which predispose to PrCa are associated with environmental factors
- To estimate the percentage of PrCa patients who have a positive family history of the disease
- To estimate the relative risk of developing PrCa in a currently unaffected member of a PrCa family
- To ascertain whether relatives of PrCa patients are at increased risk of developing cancers other than PrCa
- To determine if there are markers of PrCa that are associated with PrCa predisposition genes

- To determine if there is a specific tumour genetic profile correlated with PrCa predisposition genes

### **3 SUBJECT SELECTION CRITERIA**

#### **3.1 Inclusion criteria**

- Man with PrCa at any age at diagnosis at Royal Marsden NHS Foundation Trust
- Those outside the Royal Marsden NHS Foundation Trust with
  - PrCa at or below 60 years at diagnosis \*
  - PrCa in first or second or third -degree related pairs where one is  $\leq 65$  years at diagnosis
  - PrCa at any age in a cluster with 3 or more cases on one side of the family
- Those able to understand the information sheet and give informed consent (language line is available for those who wish to have translation)
- Any unaffected relatives of men who are already taking part in the study
- Men taking part in the CyberKnife prostate SBRT studies

\*The target of 10,000 men under this category has been achieved and as per Protocol Version 11, we would only be recruiting patients with a family history of prostate cancer as per the inclusion criteria above.

#### **3.2 Exclusion criteria**

- Man with PrCa who is too ill to take part

### **4 STUDY DESIGN**

The study is divided into two parts:

#### **4.1 The Study at The Royal Marsden NHS Foundation Trust, London and Sutton:**

The study will be offered to every patient attending the prostate clinics at The Royal Marsden NHS Foundation Trust, London and Sutton. This is called 'The Systematic Study'.

Patients are approached in the clinic and are given an information sheet and the study is also explained verbally. They are asked for 18ml of blood/saliva and asked to fill out a family history and epidemiological questionnaire. The epidemiology questionnaire is optional and data is entered and stored by Prof Ken Muir's team at the University of Manchester. Those who have not had any treatment will also be asked for 18ml blood/saliva and a urine sample for serum and plasma marker studies.

Patients who have relatives with prostate cancer and/or other cancers will be asked if their relatives can be approached to be asked to give a blood sample for DNA analysis for PrCa predisposition genes and tumour samples for molecular analyses for PrCa predisposition and behaviour as outlined above. Where relatives with PrCa are deceased, pathology records and tumour blocks will be requested after obtaining details of where they were treated via the index case.

#### *Consent*

Consent will be sought prospectively from living individuals accrued into the study from January 2006 to access medical records and tumour blocks.

This study has been active since 1992 and all blood samples have informed consent for PrCa predisposition gene studies. Outside tumour blocks and pathological samples have informed consent for molecular studies. Many of The Royal Marsden NHS Foundation Trust PrCa tumour

samples also have consent under a clause in the operation consent form in use at that time that 'material removed may be used for research purposes'. Some tissue was collected from local hospitals under the auspices of the previous protocol and the consent form did not explicitly state separate consent for the use of tissue at that time, although it was part of the approved protocol. Many patients are now deceased. It is therefore proposed that tissue and medical record data collected retrospectively will be analysed anonymously with no results fed back to patients as this would not impact upon their care. An exception is results from the studies on blood where findings in PrCa predisposition genes could have implications for relatives.

Those patients who are still living who have previously taken part in the study from 1992 until the present and who have not taken part in the environmental questionnaire part of the study will be invited to take part in this part of the study. New consent will be obtained for this.

#### **4.2 The Study at Collaborative Centres throughout the UK. Many of these are via the NCRN network.**

This is conducted as for the Study at The Royal Marsden except, the only groups of patients eligible for this part of the study are (a) men with PrCa presenting at a young age ( $\leq 60$  years)\* refer to page 14 or (b) PrCa in first, second or third-degree related pairs where one is  $\leq 65$  years at diagnosis or (c) a total of 3 or more relatives with PrCa at any age on the same side of the family

The two parts (4.1) and (4.2) are now called the UKGPCS (UK Genetic Prostate Cancer Study).

##### *Proposed analyses on the samples*

The samples will be used to find PrCa predisposition genes using molecular analyses. These investigations are solely for research to find a PrCa predisposing gene(s) and no results would be conveyed to the patients until such a gene(s) had been found. If such a gene(s) is found, then no patient will have genetic testing for abnormalities in such a gene without prior genetic counselling and this would be on a newly taken blood sample. Only those patients who wish (as stated on their consent form) to be informed of research findings will be contacted. If this occurs more than 6 months after the last contact with the patient, then contact would be via the GP.

Data will be correlated with medical records and treatment outcome to find genetic alterations that are associated with prostate cancer development and/or prognosis.

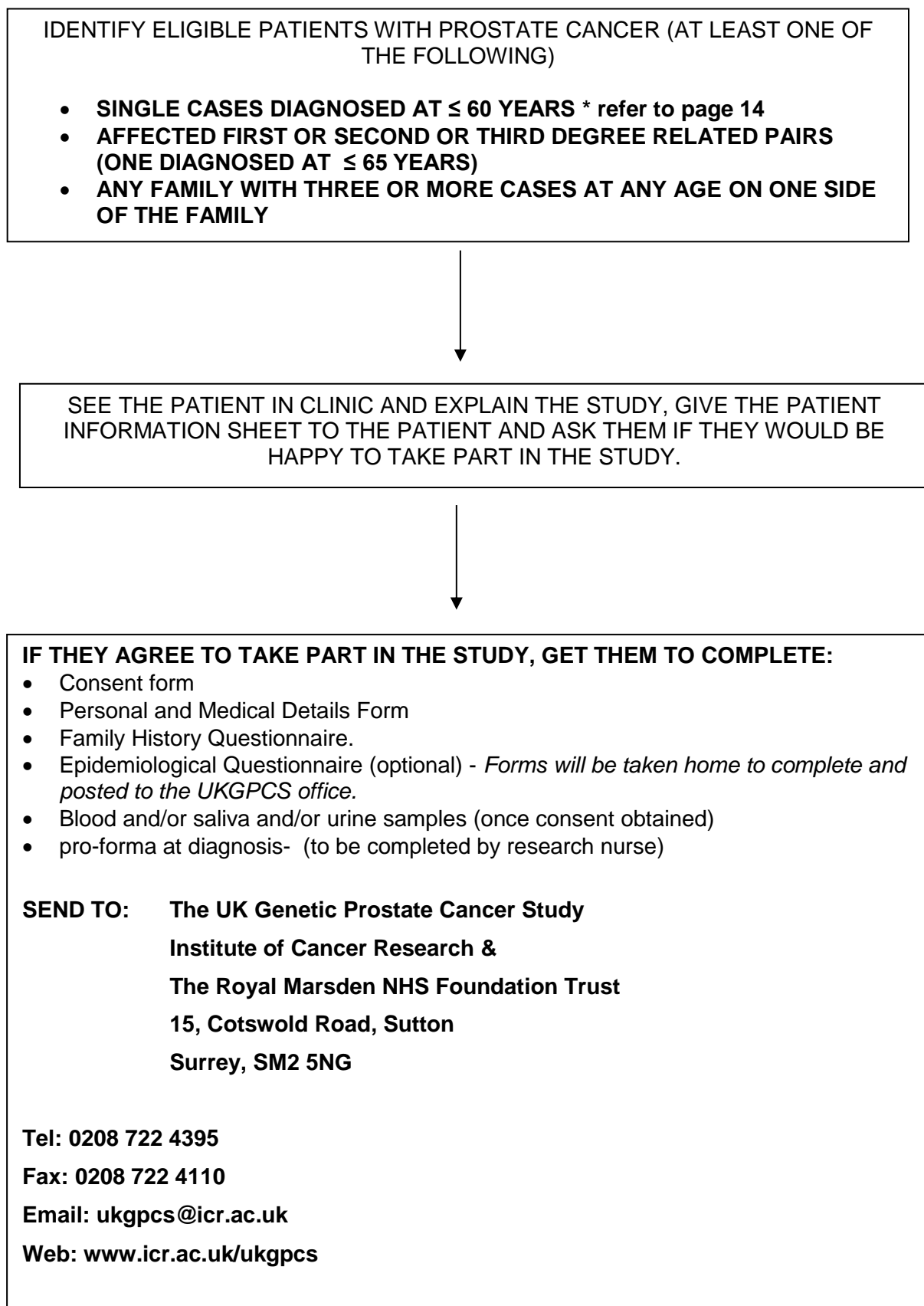
Tumour material will be collected and stored at  $-70^{\circ}\text{C}$  in freezer space currently available at The Institute of Cancer Research. Tumour will also be stored in RNA later. Paraffin embedded tumour will be made into tissue microarrays and sections cut. This will be used for molecular biology analysis. Specimens for biomarkers will be taken from untreated patients and processed in a manner suitable for future proteomic and metabolomic assays.

Cases and their relatives may be flagged by the cancer registry to confirm a diagnosis of prostate cancer, a date of death and cause of death. This will be done via the Data linkage Service (formerly known as Medical Research Information Service), using records maintained by The NHS Information Centre and the Health & Social Care Information Centre.

Clinical details are collected routinely as part of the medical care and clinical follow up record on patients with prostate cancer and these include disease parameters (e.g. stage, grade) and treatment outcome (e.g. survival data, side effects of treatment). We will also request follow-up data, approximately 2, 5 and 10 years after the patient has consented, to record any relapse, treatment and survival data that have occurred since diagnosis. We will link the genetic findings with these clinical data to try to identify genetic markers of disease parameters (e.g. those which predict for poorer prognosis or worse late toxicity from treatments such as radiotherapy). These data would be analysed anonymously after linking the clinical and genetic datasets. No overall results would be feedback to participants. We will supply anonymised data from this to other studies under an MTA (e.g the Genepi study). This would only be to a central database managed under the auspices of GCP and would only be anonymised data. No individual would be identifiable to the holders of such a database.

### 4.3 Flowchart of UKGPCS

#### WHAT THE RECRUITING CENTRES NEED TO DO





## **5 STUDY TYPE - THERAPEUTIC REGIMENS, EXPECTED TOXICITY, DOSE MODIFICATIONS**

None – this is an observational study.

## **6 POTENTIAL ADVERSE EVENTS**

Occasionally patients may be concerned about their family history and if so, we have clinically trained cancer genetic counsellors who can support them and refer them to appropriate clinical cancer genetics specialists via their GP. We also have access to psychological support counseling if an individual is distressed.

## **7 STATISTICAL CONSIDERATIONS**

For large scale empirical association studies, stringent thresholds of statistical significance are required in order to avoid false positive claims of association – a threshold of  $P < 0.0000001$  has been suggested. Large sample sizes are required to obtain this level of statistical significance for common susceptibility alleles that are likely to confer quite moderate risks of disease.

At this level of significance, 10,000 cases and 10,000 controls will provide approximately 75% power to detect an allele with a population frequency of 1% that confers a 2 fold increase risk of prostate cancer, or an allele with a frequency 5% that confers a 1.3 fold risk. These alleles would explain approximately 1% of the observed familial risk of prostate cancer, and hence are of plausible magnitude. This is therefore the target size of the systematic series.

Cases with a positive family history of prostate cancer provide greater power to detect associations since the frequency of susceptibility alleles will be higher in this group. Cases with early onset prostate cancer are also potentially more powerful since the familial risk of prostate cancer is greater at young ages. We aim to collect at least 10,000 cases of PrCa diagnosed at  $\leq 60$  years together with cases from 2,000 affected families.

Taken together, the total cases will be equivalent to approximately 26,000 cases, depending on how many cases we recruit from each affected family (we have allowed for an average of 3 cases per family to equal 6,000 familial cases). They would therefore have 75% power to detect an allele with frequency of 1% that confers a 1.5 fold increased risk of PrCa or an allele with a 5% frequency that confers a 1.2 fold risk.

Association studies will utilise these latter groups in the initial stages of analysis while using the systematic series to provide confirmation of associations and a direct estimate of the relative risk associated with any susceptibility allele. Collection of familial and early onset cases will therefore remain a priority in the study. Total numbers of PrCa cases therefore sought are:

10,000 from the Royal Marsden (The Systematic Series); 10,000 early onset cases (outside referrals with PrCa aged  $\leq 60$  years at diagnosis); approximately 6,000 cases from 2,000 families (from outside referrals).

Statistical analyses using clinical data from the Royal Marsden Foundation Trust will be specified and documented in the form of Statistical Analysis Plans in accordance with the Royal Marsden Standard Operating Procedures. These Statistical Analysis Plans will be submitted to the Royal Marsden Committee for Clinical Research (CCR) for review and approval.

## **8 INVESTIGATOR AUTHORISATION PROCEDURE**

Investigators will be authorised to register subjects in this trial only when they have returned to the Study Centre:

- A commitment statement / study acknowledgement form, indicating that they will fully comply with the protocol, to include an estimate of their yearly accrual and if any conflict of interest may arrive due to their participation in the trial,
- A copy of the letter of acceptance of the protocol by their local or national (whichever is applicable) ethics committee,
- A signed conflict of interest disclosure form: this document will be required only if a possible conflict is declared by the commitment form.

## **9 FORMS AND PROCEDURES FOR COLLECTING DATA**

Data are collected by the Study Office:

The UKGPCS Team  
Institute of Cancer Research &  
Royal Marsden NHS Foundation Trust  
15 Cotswold Road, Sutton, Surrey, SM2 5NG

Tel 020 8722 4395/4162

Fax 020 8722 4110

[ukgpcs@icr.ac.uk](mailto:ukgpcs@icr.ac.uk)

**ALL FORMS MUST BE DATED AND SIGNED BY THE RESPONSIBLE INVESTIGATOR OR ONE OF HIS/HER AUTHORISED STAFF MEMBERS.**

## **10 QUALITY ASSURANCE**

### **10.1 Control of data consistency**

Data forms will be entered in the database of the Study Data Centre at The Institute of Cancer Research and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager to be entered on the master database. Inconsistent forms will be kept "on-hold" until resolution of the inconsistencies has occurred.

## **11 ETHICAL CONSIDERATIONS**

### **11.1 Subject protection**

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Appendix A) or the laws and regulations of the country, whichever provides the greatest protection of the subject.

The protocol has been written, and the study will be conducted according to the ICH Harmonised Tripartite Guideline for Good Clinical Practice (ref: <http://www.ifpma.org/pdfifpma/e6.pdf>).

The protocol will be approved by the MREC National Ethics Committee.

## **11.2 Informed consent and feedback of results**

Consent will be sought prospectively from living individuals accrued into the study from January 2006 to access medical records and tumour blocks in addition to consent for blood, saliva, urine and other tissue samples.

This study has been active since 1992 and all blood samples have informed consent for PrCa predisposition gene studies. Outside tumour blocks and pathological samples have informed consent for molecular studies. Many of The Royal Marsden NHS Foundation Trust PrCa tumour samples also have consent under a clause in the operation consent form in use at that time that 'material removed may be used for research purposes'. Some tissue was collected from local hospitals under the auspices of the previous protocol and the consent form did not explicitly state separate consent for the use of tissue at that time. Many patients are now deceased. It is therefore proposed that tissue and medical record data collected retrospectively will be analysed anonymously with no results fed back to patients as this would not impact upon their care. An exception is results from the studies on blood where findings in PrCa predisposition genes could have implications for relatives; in these cases informed consent has been obtained from all samples being worked on in the study to date. We may request tissue samples from other members of the family where findings in PrCa predisposition genes need to be verified by further analysis of the family, or where unaffected relatives have expressed interest in taking part in the study. In the case of deceased relatives we would ask for written permission from the family to request tissue from the hospital where this was stored. In the case of a living relative we would ask this individual for written consent to obtain blood or other tissue samples to help with our research.

Those patients who are still living who have previously taken part in the study from 1992 until the present and who have not taken part in the environmental questionnaire part of the study will be invited to take part in this part of the study.

It will be emphasised that the participation is voluntary and that the subject is allowed to refuse further participation in the protocol whenever he wants. This will not prejudice the subject's subsequent care.

For European Community member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative".

## **12 ADMINISTRATIVE RESPONSIBILITIES**

### **12.1 The Study Team**

The PI, the Statistician, Study Co-ordinator and Laboratory Team Leader or their designated teams will be responsible for writing the protocol, reviewing and entering all case report forms/medical record (including the histology reports), performing molecular and statistical analyses and for writing the draft of the study results. The PI will also generally be responsible for answering all clinical questions concerning eligibility and the evaluation of the subjects.

#### ***Study Office***

The Study Office will be responsible for reviewing the protocol, collecting clinical data proformas controlling the quality of the reported data, and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the Study Office.

The UKGPCS Team, The Institute of Cancer Research, 15 Cotswold Road, Sutton, Surrey, SM2 5NG, UK  
Tel: +44 (0)20 8722 4395/4162, Fax: +44 (0)20 8722 4110, E-mail : [ukgpcs@icr.ac.uk](mailto:ukgpcs@icr.ac.uk)

## **12.2 Adverse Events Reporting**

**Safety Desk: as above or 44-7770 985331 (for telephone emergencies only) or 0207 352 8171 and ask for Prof Eeles' team (back up telephone number)**

**Fax 44-208722 4110 Mark FOR UKGPCS - Professor Ros Eeles**

The Safety Desk will forward all SAE reports within 24 hours of receipt to the PI

## **13 TRIAL SPONSORSHIP AND FINANCING**

The study is financed by

- Cancer Research UK (Programme Grants to Prof. R. Eeles)
- NIH
- NIHR
- Prostate Cancer UK
- Prof. Eeles' Research Fund
- The Institute of Cancer Research (Everyman Campaign)
- Movember

The study is sponsored by The Institute of Cancer Research

## **14 PUBLICATION POLICY**

The Principal Investigator (PI), Co-PI and the Study Team, on the basis of the final analysis performed at the Data Centre will write the final publication of the study results.

Authors of the manuscript will include at least the PI, Statistician all collaborators who have entered at least 1 study individual (until 2006, known as the CR-UK/BPG/BAUS Section of Oncology Study Collaborators). All manuscripts will include an appropriate acknowledgement section, mentioning the supporting bodies.

The PI and The Statistician must approve all publications, abstracts and presentations based on subjects included in this study.

## 15 APPENDIX A

### World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly

Helsinki, Finland, June 1964

and amended by the

29th World Medical Assembly, Tokyo, Japan, October 1975

35th World Medical Assembly, Venice, Italy, October 1983

41st World Medical Assembly, Hong Kong, September 1989

48th General Assembly, Somerset West, Republic of South Africa, October 1996

and the

52<sup>nd</sup> WMA General Assembly, Edinburgh, Scotland, October 2000

#### A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

#### B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless

the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

### **C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE**

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

## **16 APPENDIX B**

### **Inclusion of Patients from Charing Cross Hospital**

A cohort of patients currently being treated at Charing Cross Hospital and for whom we know tissue samples have already been collected for another purpose, will be able to participate in the study under the same inclusion criteria which is currently used solely for Royal Marsden Hospital patients, i.e. 'Man with PrCa at any age at diagnosis'.

The same sequence of study I.D. numbers will be used for these participants as are used for the Royal Marsden patients to save any confusion as to why they have been recruited into the study outside of the normal recruitment criteria.