

**Identification of Men with a genetic predisposition to
Prostate Cancer: Targeted Screening in *BRCA1/2*
mutation carriers and controls**

The IMPACT study

STUDY PROTOCOL

MREC REFERENCE: 05/MRE07/25

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1. BACKGROUND

Introduction

Prostate cancer is a significant public health problem. In the European Union, approximately 200,000 men are diagnosed annually with prostate cancer. There are 31,900 cases per year in England and Wales and 10,000 deaths. It is now the commonest male non-cutaneous cancer diagnosis in the UK, the lifetime risk of being diagnosed with prostate cancer is 1 in 13 (Everyman campaign, 2003; Thompson et al 2004, Cancer Research UK, 2006, The Office of National Statistics (1999)).

Multiple aetiologies have been proposed to contribute to the development of prostate cancer. Although a specific gene has not yet been established, 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, 1990; Singh, 2000; Edwards et al, 2003). A segregation analysis by Carter et al in 1992, and later by Paiss, suggested an autosomal dominant gene could account for approximately 43% of prostate cancer patients diagnosed before age 55 and 9% of cases diagnosed up to age 85 (Simard et al, 2003; Paiss et al, 2002). Prostate cancer Relative Risk (RR) rises dramatically the younger the age of the proband, as the number of cases in a family cluster increases, with a decrease in the average age of onset of cases in a cluster, and with a combination of these factors. This increase is too great to be explained by non-genetic factors, such as environment, alone. 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 lifetime risk for developing prostate cancer of 63-88%. Two cohort studies (Goldgar et al, 1994; Gronberg et al, 1997) estimated the RR of prostate cancer in first-degree relatives to be 2.2. Meta-analysis of the current literature on risk of prostate cancer 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 (Bruner et al, 2003).

Several candidate genes have been reported that may predispose to prostate cancer but the evidence from linkage analysis and cohort studies is controversial. There is a recognised association of breast cancer with prostate cancer 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 prostate cancer (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 prostate cancer 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 prostate cancer in male *BRCA2* mutation carriers (RR 7.33 below the age of 65 years) 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) with an estimated cumulative incidence by the age of 70 years of 7.5-33%. The prostate cancer risk in male *BRCA1* and *BRCA2* carriers therefore remains uncertain. Recent studies have suggested that the risk for male *BRCA1* mutation carriers may be lower than previous estimates and that *BRCA2* mutation carriers may have a significantly higher RR of 23-fold at age 60 (Edwards et al, 2003; Eeles et al 1999). Furthermore, *BRCA2* mutations may not only be involved in susceptibility to prostate cancer, but also to the aggressiveness of the disease (Sigurdsson et al, 1997, Eeles et al unpublished data, 2005)

Prostate cancer screening studies of the general population to date have not clearly shown a reduction in mortality from disease. It is apparent that prostate cancer may be identified at an earlier TNM stage but this may not translate into a survival benefit. We await the results of 3 large screening studies the European Randomised Study of Screening for Prostate Cancer (ERSPC), the ProtecT study (which looks also treatment options) in the UK and the Prostate, Lung, Colon, and

Ovarian Cancer (PCLO) study in the USA that are due to report in the next few years, but it may be that targeting screening in a high risk population proves most beneficial. (Schroder et al, 1997, Donovan et al, 2003, Crawford et al, 2006).

As the data above suggest an increased relative risk of PC in *BRCA1* and *BRCA2* carriers and also that familial PC may be more aggressive with an earlier age of onset, screening for prostate cancer in this group of men may be beneficial. It may result in the treatment of disease that would otherwise limit life-expectancy and avoid the treatment of clinically insignificant disease. Controversial recommendations from the American Urological Association and American Cancer Urological Society advise screening should be undertaken in all men over 45 years if they have a family history of prostate cancer (Dall'era 2002). No study has yet been performed to evaluate a programme of targeted screening of men with a known genetic mutation. IMPACT is the first controlled trial to address this issue in men who carry mutations in the *BRCA1* or *BRCA2* genes.

PSA Screening

Screening for prostate cancer in the general population is based mainly on the measurement of blood PSA levels. However, there is considerable uncertainty about the PSA threshold at which prostatic biopsy should be considered and whether this should vary with age, both in the normal population, and in a high-risk subset. A few reported studies of PSA screening in first degree relatives within prostate cancer clusters show an increased proportion of raised PSA levels compared with a non-targeted population. This translates into a three-fold higher detection of clinically significant prostate cancer (Mc Whorter et al, 1992; Neuhausen et al, 1997; Matikainen et al, 1999; Valeri et al, 2002). Makinen et al (2002) carried out an extensive study in the USA and surprisingly found that a positive family history did not correlate with a substantial increase in PSA level. These were all relatively small studies and though most seem to suggest value in screening a high risk population, the situation is not clearly resolved.

The optimal definition of the normal range of PSA is not clear. In the general population it has been shown that that clinically detectable prostate cancer is present in 13-20% of men within 3 to 5 years of a PSA measurement between 2.5-4.0 mg/ml and 25-30% of men with a level above 4.0ng/ml (Gann et al, 1995; Karazanashvili et al, 2003). The ERSPC study found that lowering prostate biopsy indication to a PSA cut-off of 3ng/ml or greater without a DRE improved the positive predictive value from 18.2% to 24.3%. The number of biopsies necessary to detect one case of prostate cancer accordingly changed from 5.4 to 3.4 (Schroder 2001, Gosselaar et al, 2006). The Prostate Cancer Prevention Trial (PCPT) found 15% of men with PSAs less than 4 ng/ml and a normal DRE had PC diagnosed on biopsy. In the PSA range 3.1-4.0 ng/ml 52 out of 193 men biopsied were found to have PC (26.9% of men biopsied at this range) (Thompson et al, 2004). Currently, the ERSPC and Protec T studies are using a PSA level for biopsy of 3ng/ml for screening the general population with an interval of 4 years. In our population study of male *BRCA1* and 2 carriers, we aim to screen men aged 40-69 years. The younger age group coupled with the data regarding the incidence of PC in the PSA range 3-4 ng/ml, leads us to believe that a PSA of 3ng/ml without DRE (as this does not increase sensitivity and specificity) would be the most appropriate method of screening this cohort.

Recent results from the ERSPC study using a PSA threshold of 3ng/ml without DRE in men in the *general population* aged 55-75 years found a raised PSA in 20% in the first screening round with a PC diagnosis of 5.3%. In the second round, 19% had a raised PSA and 3% were found to have PC overall. Twenty-six and twenty per cent of men with a raised |PSA in the first and second rounds respectively were found to have PC after biopsy (Roobol et al, 2006).

There are several factors unrelated to prostate cancer that can affect total PSA level such as age, race, prostatic inflammation and benign prostate hyperplasia (BPH). Although PSA sensitivity is

72-90%, its specificity is not high (Dall'era, 2002). Therefore, efforts to improve the sensitivity and specificity of serum PSA using different diagnostic parameters have been developed. These include age-adjusted PSA, free to total fraction PSA, PSA density and PSA velocity. The most applicable components of these are age-adjusted PSA and free to total PSA ratio. Oesterling et al (2001) found that PSA increases with age. Data from many different studies have shown that the mean PSA cut-off for men aged 40-49 years is 2.14ng/ml compared with 3.40ng/ml for men aged 50-59 years old. However, age adjusted PSA cut-offs are not recommended for men 60 years or older because of the danger of overlooking a significant number of prostate cancers. Thus, more recently, the concept of percentage of free PSA has been investigated to increase the specificity of serum PSA for detecting early prostate cancer. Uzzo et al (2003) have described the cancer detection rate using percentage of free PSA in a group of high risk men. This group had a normal DRE, a total PSA of between 2.0 and 4.0ng/ml, and a free PSA of less than 27% (Catalona et al, 1999; Djavan et al, 1999; Karazanashvili, 2003). These refinements to PSA screening have been applied to general population screening, but not particularly in high-risk men with specific genetic predisposition to date. Thus, it is important that these parameters are evaluated as an integral part of the screening strategy for the IMPACT study. Recently, the value of serum measurements for glandular kallikrein 2 (hK2) has been under explored in combination with the PSA ratio as a research investigation. DRE and TransRectal Ultrasound (TRUS) are thought to add little to sensitivity of screening, and are not routine screening tools used in high-risk populations.

BRCA1/2

BRCA1 and *BRCA2* genes are involved in DNA repair and cell cycling. Genetic instability is a characteristic of *BRCA1/2* deficient cells that leads to an accumulation of genomic and post-genomic abnormalities. Although microarrays give information about gene expression, there is disparity between protein expression and mRNA levels. The proteomics approach is promising as it identifies protein expression profiles and can provide data missed from expression studies due to post-translational modifications such as glycosylation.

There are four basic types of mass analyzer used in proteomics, each with its own strengths and weaknesses in terms of accuracy, sensitivity and resolution. The simplest instruments are the quadrupole and time-of-flight (TOF) analyzers. The more sophisticated are the ion trap and Fourier transform ion cyclotron analyzers. Since the controversial data from Petricoin et al, 2002, which used the TOF method, further studies have produced promising data, particularly in the area of distinguishing prostate cancer from benign prostatic disease (Petricoin 2002, Cazares 2002, Banez 2003). There is at present no consensus on the most accurate method to optimize sensitivity, specificity, accuracy and resolution. We will therefore collect serum, plasma, urine and tissue with the aim of conducting proteomics when a more robust proteomics platform is decided upon. We hope to identify protein signatures that may differentiate men with PC and those predisposed to developing PC.

Although prostate cancer tends to be a slow-growing neoplasm affecting older men, there is clearly a subset of patients at high risk for developing early and possibly more aggressive disease. This group of high-risk patients includes men with a family history of prostate cancer and various histological features such as Prostatic Intraepithelial Neoplasia (PIN) on an initial biopsy. Prostate cancer in *BRCA2* carriers affects men at a young age and may be more aggressive (Eeles, unpublished data, 2005). Therefore the optimal treatment of prostate cancer in *BRCA1* and *BRCA2* male mutation carriers is unknown. In the general population a multidisciplinary approach is used and treatment options include radiotherapy (external beam or brachytherapy), surgery, hormone therapy in combination or alone and active surveillance. No studies to date have investigated whether there is an optimal treatment strategy specifically for *BRCA1/2* carriers who develop prostate cancer. Moreover, there is an ongoing debate about the risks and benefits of radiotherapy

and the potential mutagenicity of ionising radiation in these men who may have a germline deficiency in DNA repair.

IMPACT

The IMPACT study (Identification of Men with a genetic predisposition to Prostate Cancer: Targeted screening in *BRCA1* and *BRCA2* mutation carriers and controls) has been developed to investigate the role of targeted prostate cancer screening in male *BRCA1* and *BRCA2* gene mutation carriers. It is an international collaboration that will follow up male carriers across the world. This study aims to recruit 500 men with identified *BRCA1* mutations and 350 men with *BRCA2* mutations, unaffected by prostate cancer, aged between 40-69 years. The ERSPC and ProtecT studies will provide control groups. In addition, 850 men aged 40-69 who have tested negative for a known pathogenic familial mutation in *BRCA1/2* will be recruited to provide a carefully matched control group for the targeted screening and biomarker analysis.

PSA level will be measured annually in both *BRCA1* and *BRCA2* mutation carriers and the control group who have had a negative predictive *BRCA1* or *BRCA2* test. PSA levels will be measured at the local centre and analysed at a central reference laboratory to ensure standardisation and quality assurance. Since PSA is age-dependent, the results from the male mutation carriers will be compared with age-matched controls from the European Randomised Study of Screening for Prostate Cancer (ERSPC) study in Europe and the ProtecT PSA population screening study in the UK. All individuals with a PSA of >3.0ng/ml will be offered a diagnostic ten core prostatic biopsy. The guidelines for pathological review are attached. Those cases whose first biopsy detects atypical cells or high grade PIN will be re-biopsied the former immediately and the latter at six weeks (as per the ERSPC protocol). Those men with a negative biopsy will return to annual screening and biopsy will not be repeated until PSA value increases by at least 50%. Cases with a positive biopsy will be referred to their local urologist for treatment according to local policy. The outcome of different treatments in *BRCA1/2* men with prostate cancer has not been studied, therefore patients will have 5 years' follow-up in order to compare treatment outcomes retrospectively.

There is the potential for the investigation of new modifier genes or new biomarkers in this population for which whole blood, lymphocytes, serum, plasma, urine and prostate tissue specimens will be collected for further study using biochemistry, proteomic, metabonomic and microarray approaches.

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2 AIMS AND OBJECTIVES

2.1 Aims

- To establish an international targeted prostate cancer screening study in *BRCA1* and *BRCA2* carriers and men with a negative predictive *BRCA1* or *BRCA2* test (controls) where biological samples can be taken and assessed in this cohort.
- To determine the incidence of raised PSA and abnormal biopsy as a result of PSA screening in this group and determine if the incidence of raised PSA and pathology is different from screen-detected disease in controls which comprise:
 - i) a group of men who are age matched (+/- 5 years) and who have a negative predictive genetic test
 - ii) two population based screening studies
- To determine the sensitivity and specificity of PSA screening for prostate cancer in male *BRCA1/2* gene mutation carriers and controls.
- To prospectively collect serial serum and urine samples to evaluate new markers of early prostate cancer in *BRCA1/2* carriers and controls.
- To gain a better understanding of the pathogenesis of prostate cancer in men with *BRCA1* or *BRCA2* mutations. This will be done through further investigation by genomics and post-genomic technologies (including micro-arrays, biochemistry, biological functional assays, proteomics and metabonomics).

2.2 End Points

2.2.1 Primary endpoint

- To determine the incidence, stage and pathology of screen-detected prostate cancer in *BRCA1* and *BRCA2* mutation carriers compared with the control population (predictive test negative for a known familial *BRCA1/2* gene mutation).

2.2.2 Secondary endpoints

- To determine the age-specific PSA levels in *BRCA1* and *BRCA2* mutation carriers versus controls from:
 - i) a group of men who are age matched (+/- 5 years) and who have a negative predictive genetic test
 - ii) two population based screening studies
- To determine a profile of PSA level and its predictive value for the development of prostate cancer in *BRCA1/2* mutation carriers using 5 years' annual follow up compared with the control populations
- To evaluate the sensitivity and specificity of new serum and urine markers of prostate cancer in *BRCA1/2* mutation carriers
- To develop microarrays to determine the genetic profile of prostate cancers occurring in *BRCA1* and *BRCA2* mutation carriers
- To characterize the genomic and biological profiles in samples from *BRCA1* and *BRCA2* mutation carriers and changes related to prostate cancer in those individuals.

2.2.3 Associated studies

Adjunctive psychosocial study (PI Dr C Moynihan)

3 SUBJECT SELECTION CRITERIA

3.1 Inclusion criteria

- Male carrier of a known pathogenic *BRCA1* or *BRCA2* mutation
- Male who has tested negative for a known pathogenic *BRCA1* and *BRCA2* mutation present within their family
- Age 40-69 years
- WHO performance status 0-2 (see Appendix B)
- No previous history of prostate cancer
- No previous prostate biopsy for raised PSA
- Absence of any psychological, familial, sociological or geographical situation potentially hampering compliance with the study protocol and follow-up schedule.
- Informed written consent must be sought according to ICH/EU GCP, and national/local regulations before subject registration.

3.2 Exclusion criteria

- Previous cancer with a terminal prognosis of less than five years.
- Previous prostate cancer

4. TRIAL DESIGN

This is a prospective diagnostic trial of screening for prostate cancer in *BRCA1* and *BRCA2* mutation carriers to estimate the incidence of prostate cancer and the sensitivity and specificity of PSA screening in this population. Additionally, the study aims to identify serum and/or urine markers predictive of the risk of developing prostate cancer and to characterise whether there are pathological and prognostic differences between prostate cancers developing in carriers versus controls.

4.1 Registration

The target population is a group of 850 males carrying a pathogenic mutation in the *BRCA1* or *BRCA2* genes (500 *BRCA1* and 350 *BRCA2*). A control group of 850 men who have tested negative for a known familial pathogenic *BRCA1* or *BRCA2* gene mutation will also be recruited. Eligible men will be identified through collaborating genetics clinics across the world. The consultants at collaborating centres will obtain written consent for the local research team to contact individuals expressing an interest in taking part in the study.

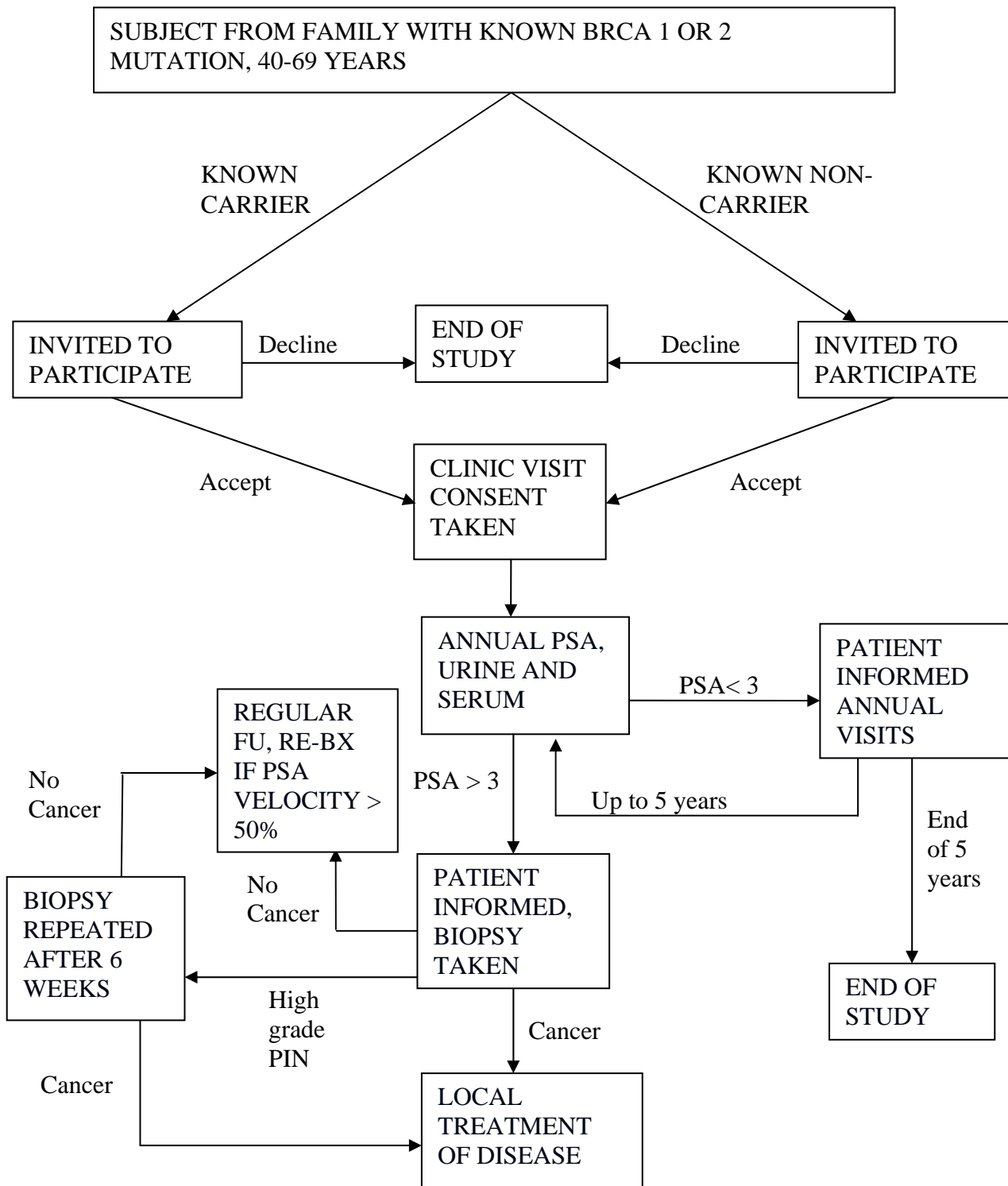
Individuals expressing interest in taking part in the study will be sent a patient information sheet (see Appendix C). This explains the study in lay terms and gives the contact details for the local research team. Individuals will be requested to complete a reply slip and those that confirm their interest will be telephoned by the local research team to confirm eligibility and make an initial appointment. During this appointment fully informed written consent will be sought (see Appendix D) before collecting any research samples. The participant will have the choice of attending an appointment at their local centre, at a different collaborating centre or for the local research team to visit them in their home. This will depend on the collaborating consultants' preference and patient convenience.

The appointment will last approximately 30 minutes during which the participant will have the opportunity to discuss the study in detail before giving their written consent. They will have a 50ml blood sample taken and be asked to provide a urine sample. They will also be asked to complete a family and medical history questionnaire (See Appendices E and F).

The PSA level of all participants will be measured locally and in a reference lab. If this is found to be $>3.0\text{ng/ml}$, they will be asked to have a ten core prostatic biopsy for diagnostic purposes (with 2 further samples being taken for research). Consent to take the 2 extra samples for research will be sought before the biopsy procedure commences. If any of the ten cores identify the presence of prostate cancer, the subject will receive treatment as advised by their local centre. If the biopsy is normal their PSA will be measured in 12 months time. The protocol for biopsy procedure is Appendix G. If high-grade PIN is found, or an inconclusive biopsy is obtained it will be recommended that a sextant biopsy will be repeated after 6 weeks. Based on community screening studies, 8-12% of men in the study age group (40-69 years) will have a PSA greater than 3.0ng/ml , and 2.5-4.3% will have prostate cancer.

The study will also investigate the stage distribution of detected cases and the interval cancer rate. The primary endpoint is prostate cancer incidence as determined by biopsy. Incidence will be analysed by time-to-event analysis, excluding subjects diagnosed with prostate cancer in the six months from first screen. We will recruit 850 men from the target population (350 *BRCA2* and 500 *BRCA1* mutation carriers) and intend to follow them for 5 years in the study and a further 5 years thereafter. 850 men from the control population will be recruited. At entry to the study we could expect to detect 60 prostate cancers in each cohort, based on the risk estimates above, but the increased relative risk of cancer in the study population may increase this. In the years following enrolment, the annual event rate may be as low as 1%. We will also seek to define the age-specific ranges for PSA in this population and to compare them with the ERSPC values.

4.2 Algorithm of Study entry



5. THERAPEUTIC REGIMENS, EXPECTED TOXICITY, DOSE MODIFICATIONS

This is a screening study and so all interventions are outlined in section 6 below.

6 CLINICAL EVALUATION, LABORATORY TESTS AND FOLLOW-UP

6.1 At enrolment

Each subject will complete the following:

- Sign the study consent form after reading the patient information sheet and after having chance to discuss the study and have questions answered by a member of the research team (Appendices C and D).
- Family history of cancer will be taken (Appendix E) if this information has not been collected and available in medical records
- Medical history questionnaire completed (Appendix F). He will then undergo a general clinical examination by a participating doctor at his local centre.
- 50ml blood sample and urine sample taken for total PSA level and other studies (Appendix H – Guidelines for Sample Collection)
- Anti-coagulated plasma and venous blood for lymphocyte, DNA and RNA extractions and storage will be collected in those centres with the facilities to process such samples

The results of the local PSA blood test will be disclosed to the subject.

6.2 On annual review

Medical and family history will be updated, and then each subject will undergo PSA testing and serum, plasma and urine storage.

6.3 If PSA is above 3ng/ml

All subjects with PSA level $>3.0\text{ng/ml}$ will be offered transrectal ultrasound and ten core biopsy, performed according to the study guidelines (see appendix G). Prior to the biopsy consent will be sought to obtain two additional research biopsies (optional for patient) which will be snap frozen for future DNA and RNA analyses. These two biopsies will be taken after all clinically indicated biopsies have been taken and only if the subject agrees to continue the procedure at the time.

All biopsies will be reviewed by a central team of pathologists in each country using an agreed standardised procedure (See Appendix I). Management of the subject following this biopsy is as directed by his local uro-oncology unit. If PIN (prostatic intraepithelial neoplasia) is diagnosed or the biopsy is inconclusive, the biopsy will be repeated at 6 weeks. Repeat biopsies do not exclude the subject from this study.

If the biopsy is negative and there is no clinical concern that this or the PSA should be repeated, the subject will return to annual screening. Biopsy need not be undertaken again unless the PSA value increases by at least 50%.

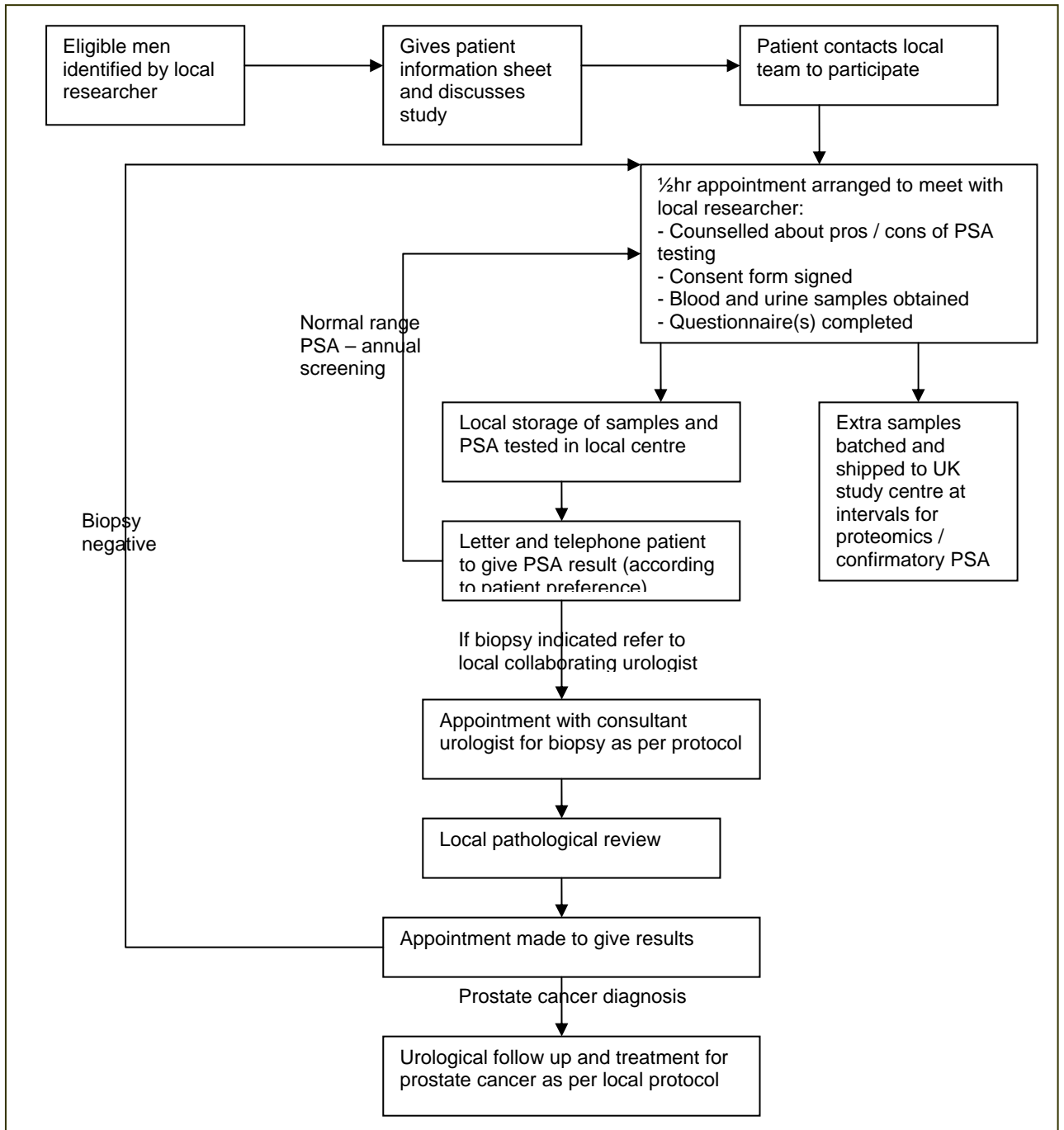
6.4 If prostate cancer is diagnosed

The staging and further investigation of the disease is as directed by the collaborating uro-oncology unit. Management is based on the immediately available pathology report, not on the later central review.

Minimum information required by the study centre will be:

- Clinical T stage (Appendix J)
- Gleason grade of biopsy and extent of involvement (Appendix J)
- Treatment and management plan (Appendix K)
- Radiological TNM stage
- Histopathology report
- Slides should be sent for central review after the local clinical report has been issued.
- Following a diagnosis of prostate cancer, treatment forms will be sent to the trial centre annually.
- Survival will be monitored but the number of prostate cancer deaths is unlikely to be sufficient for statistical analysis.

6.5 Diagrammatic Summary of Study Entry



6.6 Potential adverse events

Transrectal ultrasound and biopsy should be carried out according to protocol (Appendix G)
This procedure is uncomfortable and associated with the following risks

- Painful or difficult voiding 13%
- Haematuria 11%
- Fever/sweats 6%
- Septicaemia 3%
- Acute urinary retention 1%

(Taken from Crundwell et al, 1999)

For this reason subjects will be followed carefully and be able to contact the urology department in case of problems.

6.7 Removal from the study

Subjects may withdraw from the study at any time if they so wish without giving a reason. Data will be censored if participants develop prostate cancer or if for other reasons they are too unwell to attend for screening (see Appendix L for discontinuation form).

7. CRITERIA OF EVALUATION

- This is a screening study whose endpoint is the incidence of prostate cancer in the screened population.
- PSA level will be reported annually
- All biopsy interventions and results will be reported to the trial centre as they occur. Biopsy results will be reviewed by a central team of pathologists.
- Prostate cancer diagnosis will be reported immediately. The diagnosis and treatment will be based on histological confirmation. A later research central review will be undertaken by a central team of pathologists. If there is disagreement the local diagnosis will be the overriding one for treatment.
- Adverse events, particularly relating to trial related biopsies, will be recorded
- Cause of death will be reported by the participating centre and verified from cancer registry data.
- Initial translational studies will use the stored serum samples and will include assays for free:total PSA levels and human kallikrein 2 (hK2) and proteomics and other markers for research only.

8. STATISTICAL CONSIDERATION

8.1 Statistical design

8.1.1 Sample size

Assuming that the age-distribution of carriers at entry is distributed uniformly over the age-range 45-69 (the only age range on which data are available), then the cancer detection rate, based on the ERSPC trial, approximately averaged over 45-69 will be approximately 27 per 1000 at the prevalence screen (For this calculation, we estimated the detection rate in the age-range 40-54, which was not included in the ERSPC trial, is equal to the detection rate in the 55-59 group reduced in proportion to the background incidence rate). The detection rate at annual screens is more difficult to estimate since the ERSPC trial used an (approximately) 4 year screening interval. Based on the detection rate for the second round the expected number of further cancers detected would be approximately 28 per 1000 men. Since the rate of interval cancers was very low in the

ERSPC trial (0.4 per 1000), this is only a slight underestimate of the expected number based on annual screening. Therefore, based on the ERSPC protocol, approximately 6% of controls would have cancers detected over the period of the study.

On the basis of the BCLC studies, the predicted relative risk for prostate cancer in this age-group is approximately 5 fold for *BRCA2* mutation carriers and 2 fold for *BRCA1* mutation carriers. To detect a two fold increased risk in the screened group, with 80% power at the $P < .01$ level, would require approximately 450 cases and 450 controls. To detect a 5 fold risk would require approximately 70 carriers and 70 controls. Allowing for a 10% drop out rate, the study will therefore aim to enrol 500 *BRCA1* carriers and 500 non-carrier controls. Over the same period approximately 350 *BRCA2* carriers and 350 controls will be enrolled.

8.1.2 Randomisation and stratifications

No randomisation is planned

9. INDEPENDENT DATA MONITORING COMMITTEE

An IDMC will be appointed.

10. QUALITY OF LIFE ASSESSMENT

Quality of life will not be assessed in this study. However psychosocial issues will be addressed in an associated study. (PI Dr Clare Moynihan).

11. ECONOMIC EVALUATION

No economic evaluation will be performed in this study.

12. TRANSLATIONAL RESEARCH

The translational research studies aim to:

Investigate new serum markers of prostate cancer and of familial predisposition

Study germline and somatic gene expression (blood and tumour RNA studies)

Immunophenotyping of prostate cancer specimens to identify histopathology features of *BRCA1/2* carriers versus control group.

13. INVESTIGATOR AUTHORISATION PROCEDURE

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

- The Researcher Agreement of Responsibilities (Appendix P).
- The Material Transfer Agreement (Appendix Q).
- A copy of the letter of acceptance of the protocol by their local or national (whichever is applicable) ethics committee,

And, if the following documents are not yet available at the Data Centre:

- Updated Curriculum Vitae,

- List of their staff members authorised to sign case report forms, with a sample of each authorised signature.

14. FORMS AND PROCEDURES FOR COLLECTING DATA

14.1 Case report forms and schedule for completion

Data will be reported on the **Study Forms** and sent to:

Miss Elizabeth Bancroft
Research Nurse
Cancer Genetics Unit
Institute of Cancer Research
15 Cotswold Road
Sutton, Surrey
SM2 5NG

Case report forms (CRFs) must be completed according to the following schedule:

A. Before the study starts:

The subject must be a registered patient at the local centre. (It is not necessary to register the patient with the data centre.)

The patients eligibility should be confirmed prior to study registration.

B. At entry to the study:

The following set of forms must be completed:

- Medical History Questionnaire (by patient)
- Consent form (by patient)
- If no pedigree is available for the family, the family history questionnaire should be completed
- The CRF (Appendix O) section for the appropriate year should be completed by the researcher
- A copy of the gene report should be obtained

C. If biopsy is indicated

The following set of forms must be completed:

- Biopsy consent form
- Copy of histopathology report
- The relevant section of the CRF should be completed
- Any adverse event form (see Appendix M)

D. If cancer is diagnosed

Treatment questionnaire completed at diagnosis and updated annually for 10 years (Appendix K)

E. Upon occurrence of a Serious Adverse Event

- A serious adverse event form (Appendix M) must be completed and returned to the Data Centre within 10 calendar days of the initial observation of the event.

ALL Forms must be dated and signed by the patient / responsible investigator or one of his/her authorised staff members

14.2 Data flow

The case report forms (CRF – see Appendix O) must be completed and signed by the investigator or one of his/her authorised staff members as soon as the requested information is available, according to the above described schedule. The list of staff members authorised to sign case report forms (with a sample of their signature) must be sent to the Data Centre by the responsible investigators before the start of the study.

In all cases, it remains the responsibility of the investigator to check that original case report forms are sent to the Data Centre and that they are completely and correctly filled out. The original copy must be immediately returned to the Data Centre and the investigator must keep a copy.

The Data Centre will perform consistency checks on the CRFs and queries will be issued in the case of inconsistent data.

The local centre will keep copies of all the original documents and send photocopies to the data centre.

15. REPORTING ADVERSE EVENTS

15.1 Definitions

Adverse Events (AE) are any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs following participation in the trial regardless of the causal relationship. This can include any unfavourable and unintended signs or symptoms, an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the use of the study

- death
- a life-threatening event (i.e. the subject was at immediate risk of death at the time the reaction was observed)
- hospitalisation or prolongation of hospitalisation
- persistent or significant disability/incapacity
- any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed above).

15.2 Reporting procedure

15.2.1 Non-serious adverse events

All Adverse Events (AE) occurring during the study until the end of the period of follow-up must be recorded on the adverse event forms.

The local investigator will decide if those events are related to the study intervention (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the adverse event forms. AE definitely not study related (i.e. reported as unrelated)

will not be considered as adverse events in study analyses, but reported separately. The assessment of causality is made by the investigator using the following definitions:

| Relationship | Description |
|---------------------|---|
| UNRELATED | There is no evidence of any causal relationship |
| UNLIKELY | There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the subject's clinical condition, other concomitant treatments). |
| POSSIBLE | There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the subject's clinical condition, other concomitant treatments). |
| PROBABLE | There is evidence to suggest a causal relationship and the influence of other factors is unlikely. |
| DEFINITELY | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. |
| NOT ASSESSABLE | There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship. |

15.2.2 Serious adverse events

All Serious Adverse Events (SAE), related or not to the study treatment, occurring during the study period and within 30 days after the last study intervention (eg. biopsy), must be reported to the Data Centre.

PLEASE MARK URGENT AND FAX THE REPORT TO:

The IMPACT Data Centre
 Cancer Genetics Unit,
 Institute of Cancer Research/Royal Marsden NHS Trust,
 Downs Road,
 Sutton,
 Surrey SM2 5PT UK
 Fax.No.44-208 770 1489

The Data Centre will forward all Serious Adverse Event reports within 24 hours of receipt to all appropriate persons. To enable the Data Centre to comply with regulatory reporting requirements, completed documentation of any reported serious adverse events or serious adverse drug reactions must be returned within 10 calendar days of the initial report. If the completed form is not received within this deadline, the Data Centre will make a written request to the investigator.

PLEASE SEND THE ORIGINAL REPORT TO:

The IMPACT Data Centre
Cancer Genetics Unit,
Institute of Cancer Research/Royal Marsden NHS Trust,
Downs Road,
Sutton,
Surrey SM2 5PT UK

It should be recognised that Serious Adverse Events (SAE) which are not documented in this protocol, or which occur in a more severe form than anticipated (i.e. they are 'unexpected'), are subject to rapid reporting to the Regulatory Authorities by the sponsor/promoter. These must therefore be faxed to the data-centre within 48 hours of the event.

Any question concerning SAE reporting can be directed to:

Elizabeth Bancroft / Dr Anita Mitra
The IMPACT Study Co-ordinators
Cancer Genetics Unit
Institute of Cancer Research
15 Cotswold Road
Sutton, Surrey
SM2 5NG

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

16. QUALITY ASSURANCE

16.1 Control of data consistency

Data forms will be entered in the database of the Data Centre by a double data entry procedure. Computerised 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

16.2 External review of histology

Histological assessment of prostate biopsies is subject to inter observer variation, particularly with reference to assessing Gleason grade. For this reason biopsies will routinely be reviewed and representative samples should be sent to the central panel of pathologists for review. Clinical decisions should be based on local assessment and a routine review to confirm diagnosis is not required.

16.3 Other central review procedures

PSA testing will be repeated at the study centre designated laboratory (EURO/DPC) and results compared with the study centre values. However clinical decisions are to be made on the basis of investigation results at the cooperating centre. Free:total PSA testing will be done centrally as a research project but the results will not be available for clinical use.

17. ETHICAL CONSIDERATIONS

17.1 Subject protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) 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 Local, Regional or National Ethics Committees.

17.2 Subject identification

The name of the subject will neither be asked for nor recorded at the Data Centre, except for in the UK. A sequential identification number will be automatically attributed to each subject registered in the trial. This number will identify the subject and must be included on all case report forms. In order to avoid identification errors, subjects' initials (maximum of 4 letters), date of birth and local chart number (if available) will also be reported on the case report forms.

17.3 Informed consent

All subjects will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he will be exposed, and the mechanism of treatment allocation. He will be informed as to the strict confidentiality of his patient data, but that his medical records may be reviewed for trial purposes by authorised individuals other than their treating physician. An example of a subject informed consent statement is given as an appendix to this protocol (Appendix D).

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. Documented informed consent must be obtained for all subjects included in the study before they are registered at the Data Centre. This must be done in accordance with the national and local regulatory requirements.

For European Union 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".

18. ADMINISTRATIVE RESPONSIBILITIES

18.1 The PI and study coordinator

The PI and Study Coordinator (in cooperation with the Data Centre) will be responsible for writing the protocol, reviewing all case report forms and documenting his/her review on evaluation forms, discussing the contents of the reports with the Data Manager and the Statistician, and for writing the draft of the study results. The PI will also generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the subjects.

Study coordinators:

Elizabeth Bancroft, Cancer Genetics Unit, ICR & RMH, Downs Road, Sutton, Surrey, SM2 5PT, Tel: +44 (0)207 808 2136, Fax: +44 (0)20 8770 1489, E-mail: elizabeth.bancroft@rmh.nhs.uk

Dr Anita Mitra, Cancer Genetics Unit, ICR & RMH Downs Road, Sutton, Surrey, SM2 5PT, UK Tel: +44 (0)207 808 2136, Fax: +44 (0)20 8770 1489, E-mail: anita.mitra@icr.ac.uk

The Data Centre

The Data Centre will be responsible for reviewing the protocol, collecting case report forms, 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 Data Centre.

| | |
|----------------------------------|--|
| Registration of subjects: | Elizabeth Bancroft +44 207 808 2136 |
| | Dr Anita Mitra +44 208 661 3896 |
| Statistician: | Prof Douglas Easton (enquiries via Dr Eeles) +44 207 808 2136 |
| Research Nurse: | Elizabeth Bancroft +44 207 808 2136 |
| Clinical Research Fellow: | Dr Anita Mitra +44 208 661 3896 |
| Medical Advisor: | Dr Ros Eeles +44 208 661 3642 |
| Safety Desk: | 44-7770 985331 (for telephone emergencies only) |
| Fax: 44-208 770 1489 | Mark URGENT FOR IMPACT STUDY RESEARCH NURSE |

The Safety Desk will forward all reports within 24 hours of receipt to the Study Coordinator and the Data Manager, and will take in charge regulatory reporting.

18.2 The cooperative group

All questions concerning membership in the cooperative group should be addressed to the PI

19. TRIAL SPONSORSHIP AND FINANCING

The Sponsors of the study are:

- Cancer Research UK (Research Nurse and Statistical Support)
- The Ronald and Rita McAulay Foundation (Clinical Research Fellow)
- Sponsorship is being sought for local support for study entry

20. TRIAL INSURANCE

Liability rests with the study sponsor – the Institute of Cancer Research and all national and international collaborating centres are required to agree to the Research Agreement of Responsibilities (see Appendix P) and the Material Transfer Agreement (see appendix Q).

21. PUBLICATION POLICY

The Study Coordinator and Principal Investigator, on the basis of the final analysis performed at the Data Centre will write the final publication of the study results. A draft manuscript will be submitted by the study coordinator to the Data Centre for review no later than six months after receiving the Data Centre report. After revision by the Data Centre and other co-authors the manuscript will be sent to a major scientific journal.

Authors of the manuscript will include at least the Study Coordinator; the Principal Investigator and Steering Committee, Research Nurse and all collaborators who have entered at least 1 study individual (the numbers entered by each centre will be included in the publication information). If the group wishes to publish or present study data before this final publication, the approval of the steering committee will be sought

All publications, abstracts or presentations including data from the present trial will be submitted for review to the steering committee and Data Centre prior to submission. All manuscripts will include an appropriate acknowledgement section, mentioning all investigators who have contributed to the trial, as well as supporting bodies.

The PI, the Study Coordinator and the Data Centre must approve all publications, abstracts and presentations based on subjects included in this study. This is applicable to any individual subject registered in the trial, or any subgroup of the trial subjects.