Cancer Research UK Bladder Cancer Group

BLADDER CANCER PROGNOSIS PROGRAMME

Incorporating

'SELENIB' TRIAL

Protocol

(BCPP 2005-01)

FINAL VERSION 9.0 June 2019

PLEASE DESTROY ALL PREVIOUS DRAFTS

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A programme of research

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TABLE OF CONTENTS

List of Figures

List of Tables

ABREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BCPP	Bladder Cancer Prognosis Programme
CI	Confidence Interval
CIS	Carcinoma in situ
CRCTU	Cancer Research UK Clinical Trials Unit, University of Birmingham
CRF	Case report form
CR UK	Cancer Research UK
CTA	Clinical Trial Authorisation
EORTC	European Organisation for Research and Treatment of Cancer
ECG	Electro-Cardio-Gram
EAU	European Association of Urology
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good Manufacturing Practice
HBRC	Human Biomaterials Resource Centre
HRQL	Health-related quality of life
IARC	International Agency for Research on Cancer
ICH GCP	International Conference on Harmonisation in Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
ISUP	International Society of Urologic Pathology
MHRA	Medicines and Healthcare Products Regulatory Authority
NCRI	National Cancer Research Institute
NTRAC	National Translational Cancer research Network
OR	Odds Ratio
PI	Principal Investigator (lead investigator at each site)
SOP	Standard operating procedure
SAE	Serious Adverse Event
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCC	Transitional cell carcinoma
TSC	Trial Steering Committee
TURBT	Transurethral resection of bladder tumour
US NCI	United States National Cancer Institute
VPN	Virtual private network
WHO	World Health Organization

SECTION 1: INTRODUCTION AND STUDY SUMMARY

1.1. Programme Background

Bladder cancer is the fifth most common cancer in the UK with over 12,000 new cases and 5,000 deaths per year.[1] Worldwide, there are approximately 330,000 new cases and 130,000 deaths per year.[2] In Europe and North America 80-90% of bladder cancers are transitional cell carcinomas (TCCs) of urothelial origin.[3-4]

Approximately 70% of TCCs present as stage Ta, Tis or T1 (non-muscle-invasive or "superficial").[5-7] Treatment of these conditions relies upon a thorough initial staging resection of the bladder tumour (TURBT), followed by regular cystoscopic surveillance. Optimal additional treatment comprises intravesical chemotherapy (e.g. mitomycin C) within 24 hours of TURBT and/or a course of further mitomycin C or intravesical BCG, which reduce risk of recurrence and progression respectively.[8-11] Despite these treatments the risks of recurrence and progression remain high. It is estimated that, excluding solitary grade 1 pTa tumours, the rates of recurrence and progression are about 50-60% at five years.[12] This means that at any one time in the UK 70,000 – 80,000 patients with TCCs are at risk of recurrence.[12]

In the US, bladder cancer is the fifth most expensive cancer in terms of health care expenditures.[13] It also has the highest cost per patient from diagnosis to death among all cancers in the Medicare system.[14] In the UK individual patient management is more costly for bladder cancer but less is invested in research than for prostate cancer (BJU International 2005; 95: 59-63). The impact of recurrence and progression are thus significant, both for the patients in terms of quality of life and for the NHS in terms of costs. There is therefore an urgent need for effective interventions that reduce the risk of recurrence and progression, and for a prognostic tool that could predict adverse outcomes. These interventions and markers could potentially bring about health gains in a very large number of patients. Apart from the direct benefit to patients, the reduction in frequency of cystoscopic surveillance would bring huge healthcare savings.

1.2. Programme Overview

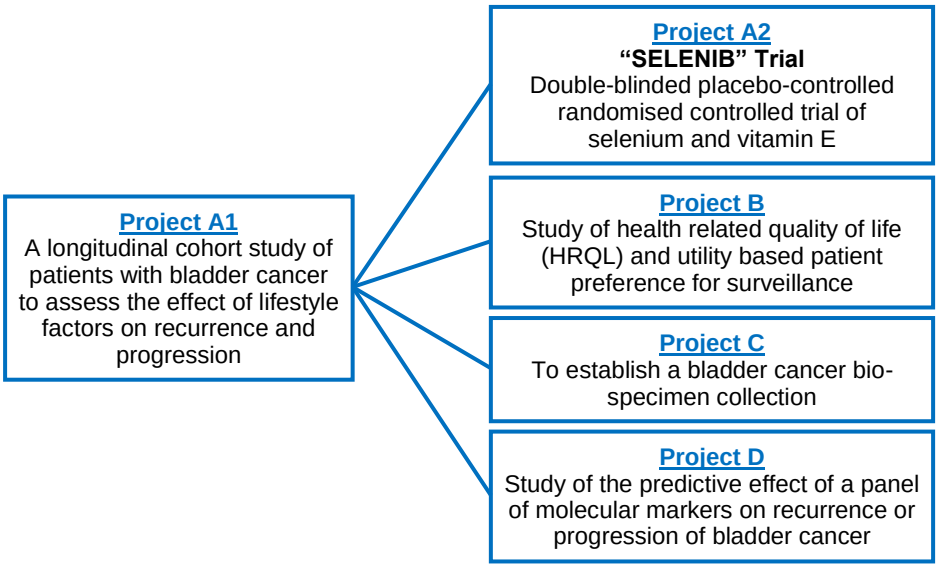
Objectives

1. To assess the effect of lifestyle factors (such as smoking, dietary habits, fluid intake and environmental exposures) on the recurrence and progression of bladder cancer
2. To study health related quality of life and its association with recurrence and progression of bladder cancer
3. To establish a collection of bladder cancer biospecimens (that will comprise blood, urine, and bladder tissue).
4. To study the predictive effect of molecular markers on the recurrence and progression of bladder cancer.

Methods

The study will be based on a cohort of patients with newly-detected bladder cancer in up to 16 urological centres within the West Midlands, commencing in late 2005 for a period of 20 years.

Figure 1: BCPP programme overview



N.B. Both muscle invasive and non-muscle invasive bladder cancer patients will be recruited into the BCPP cohort. However, the analysis of Projects A1, A2 and D will focus mainly on the non-muscle invasive subgroup. See section 2.3.1 for further details.

Primary Endpoints

1. Recurrence of bladder cancer
2. Progression of bladder cancer

Inclusion Criteria

- Disease characteristics – Bladder lesion with cytological evidence of high grade malignant cells, cystoscopic or imaging characteristics compatible with urothelial cancer/TCC or an incidental finding at rigid cystoscopy
- Able to give informed consent
- Age – 18 years or above
- Gender – both
- Fit for cystoscopy and surgical biopsy/resection

Exclusion criteria

- Previous diagnosis of cancer of the urethra, bladder, uretor or renal pelvis within the 10 years prior to current diagnosis
- Diagnosis of HIV infection
- Any condition, which, in the opinion of the local investigator, might interfere with the safety of the patient or evaluation of the study objectives

Data collection

Baseline questionnaire

- Socio-demographic data
- Health related behaviours questionnaire
- Medical history and medications
- Health related quality of life questionnaire (HRQL)
- Social support questionnaire

Self completion questionnaire (prior to first follow-up)

- Food, fluid and micturition diary
- Occupational and residential history
- Family history of cancer

Follow-up questionnaire (At 3m, 1yr, 2yr, 3yr, 4yr and 5yr post surgery)

- Changes to health related behaviours follow-up questionnaire
- Changes to medical history and medications
- Health related quality of life questionnaire (HRQL)
- Utility based patient preference for surveillance questionnaire

Case report forms (CRF's)

- Clinical treatment data
- Histological data
- Follow-up data
- Event data (recurrence, progression or death)

Biospecimen collection

- Samples of snap frozen & paraffin-embedded bladder tissue, blood, and urine (taken at diagnosis)
- Toenail clippings for baseline selenium level determination

Long-term follow-up

- Beyond the 5-years of active follow-up for recurrence, progression and mortality carried out by the BCPP office, we intend (with the right approvals) to follow-up this cohort of patients in the very long-term with regard to mortality via Public Health England (PHE) Birmingham (formerly the West Midlands Cancer Intelligence Unit).

SECTION 2: PROJECT A1: LONGITUDINAL COHORT STUDY OF DIETARY, LIFESTYLE AND ENVIRONMENTAL FACTORS

The Effect of Environmental Exposures, Diet, Lifestyle and Other Factors on Recurrence and Progression of Bladder Cancer: A Longitudinal Cohort Study

2.1. Background

The main causes of TCCs in developed countries are cigarette smoking and occupational exposure to carcinogens.[15] Genetic susceptibility may also play an important role, as reflected by the large variation in incidence between ethnic groups and also among populations with similar exposures to smoking and occupational carcinogens.[16] There is also evidence on the protective effects of other exposures, such as the dietary intake of selenium and vitamin E.

On the question of recurrence and progression, there is almost no information on the importance of environmental exposures in determining risk. Unlike malignancies that often present at advanced stages and/or have rapidly progressive courses (e.g. pancreatic, oesophageal, lung), the natural history of non-muscle-invasive TCC provides larger scope for intervention to limit the risk of adverse outcomes. In addition to investments in novel pharmaceutical interventions, modification of environmental exposures by dietary supplementation and lifestyle changes could result in substantial benefits.

2.1.1. Smoking

Evidence from epidemiological studies has shown that cigarette smoking substantially increases the risk of bladder cancer. It has been estimated in a recent meta-analysis of 43 published studies that current cigarette smokers have an approximately threefold higher risk of bladder cancer than non-smokers.[17] The Netherlands Cohort study[18] found that the association of cigarette smoking with bladder cancer risk was largely attributable to duration of smoking. In a large case control study in the West Midlands, Sorahan et al also found that stopping smoking led very quickly to reduction of risk.[19] These results may indicate that the promoting activity of cigarette smoke is of more importance than the initiating activity and consequently that cigarette smoking may also influence the progression of bladder cancer.

Health benefits in stopping smoking are unquestionable and brief advice is already given in most urology centres to newly diagnosed bladder cancer patients who smoke. Such a practice will continue in this project. However, one should bear in mind that cancer diagnosis represents a major life event. Therefore, stronger evidence that stopping smoking would

improve prognosis is likely to be needed before widespread introduction of *intensive* cessation support for smokers newly-diagnosed with bladder cancer.

The following summary of the role of other risk factors is extracted from a recent comprehensive review of bladder cancer epidemiology.[20]

2.1.2. Diet

Fruit and Vegetables

Most observational studies that investigated the consumption of fresh fruits and vegetables have shown a protective effect against development of bladder cancer.[21] A meta-analysis of 10 epidemiological studies reported an increased risk of bladder cancer associated with diets with a low fruit content (RR=1.40, 95%CI: 1.08, 1.83).[22] Regarding vegetable consumption, the same authors provided a meta-OR of 1.16 (95%CI: 1.01, 1.34) associated with diets low in vegetable content, based on 12 studies.

Meat

The effects of fat and meat intake were also summarized in a meta-analysis.[22] Elevated risks were identified for diets with a high fat content (RR=1.37, 95%CI: 1.16, 1.62) but not for diets with a high meat content (RR=1.08, 95%CI: 0.82, 1.42). Whether energy intake mostly accounts for this excess risk has not been elucidated. Only one case-control study has investigated the effect of heterocyclic amines (carcinogens arising from the cooking of meat and fish at high temperatures) and failed to find a relationship with bladder cancer. [23]

Vitamins and minerals

Six prospective cohort studies have investigated the association between serum or toenail selenium and bladder cancer incidence. [24-29] We have previously reviewed the results from five of them[28]. In the largest of these (the Netherlands Cohort Study: 120,852 men and women followed up for up to 7 years, resulting in 431 bladder cancer cases), we showed a significant inverse association between baseline selenium and subsequent bladder cancer risk. The rate ratio for the top vs bottom quintile of toenail selenium levels was 0.67 (95% CI 0.46-0.97), with a statistically significant linear trend over the five quintiles. This association was particularly strong in muscle-invasive tumours, indicating that selenium might be associated with cancer progression. Apart from smoking, selenium was the only important environmental exposure identified to be significantly associated with bladder cancer risk in this large cohort study, thus strengthening the possibility that the relationship is causal on the ground of specificity. [28] Of the other four studies [24-27], three [24-26] reported reduction in risk associated with higher baseline selenium but their powers were limited by a relatively small number of cases (92 cases in

total). The fourth of these studies found a non-significant positive association in women (based on only 9 cases) and a non-significant negative association in men (26 cases) between selenium level and bladder cancer incidence.[27]

A meta-analysis did not find increased risks for diets low in retinol (RR=1.01, 95%CI: 0.83, 1.23) or beta-carotene (RR=1.10, 95%CI: 0.93, 1.30).[31] There is no evidence that dietary or supplement intake of potassium, sodium, calcium, magnesium, phosphorus, iron, vitamin B1, B2, B6 and B12, niacin or folic acid affect UBC risk based on the results of the prospective Health Professionals Follow-Up Study in USA. [32]

2.1.3. Total fluid intake

The urogenous-contact hypothesis (or "field cancerisation" hypothesis) of transitional cell carcinogenesis associates the initiation and progression of bladder cancer with prolonged exposure to urinary carcinogens.[33-34] High consumption of fluids may reduce this exposure by diluting the urine and reducing contact time through increased frequency of urination. Among epidemiological studies, the large Harvard Health Professional Study[35] reported a negative association between high fluid intake and subsequent bladder cancer risk but the finding was not replicated elsewhere.[36;37] Only one study evaluated the association between fluid intake and bladder cancer prognosis and found no relationship. However, power was limited by the relatively small sample size.[38] One of the reasons for these inconsistent findings could be the differential roles of different types of beverage.

2.1.4. Alcohol drinking

Many studies have evaluated the role of alcoholic beverage consumption on bladder cancer risk and have provided inconsistent results. A recent meta-analysis indicated no effect for alcohol consumption on bladder cancer risk.[39] The analysis was based on 16 studies, the summary ORs for alcohol consumption being 1.3 (95%CI: 0.9, 2.0) for men and 1.0 (95%CI: 0.6, 1.7) for women.

2.1.5. Coffee drinking

The role of coffee in bladder cancer is not clear in spite of several epidemiological studies. In 1991, an IARC working group concluded that coffee is possibly carcinogenic to the human urinary bladder, though the possibilities of a bias or an influence of confounding factors (i.e. tobacco) could not be excluded.[40] Zeegers et al, in a meta-analysis, found an adjusted summary ORs for current coffee consumption of 1.26 (95%CI: 1.09, 1.46) for 16 studies in men, 1.08 (95%CI: 0.79, 1.46) for 12 studies in women and 1.18 (95%CI: 1.01, 1.38) for 14 studies with men and women combined.[36] A pooled analysis of 10 case-control studies

conducted in Europe including only non-smokers, found an excess risk for heavy coffee drinkers (OR=1.8, 95%CI: 1.0, 3.3).

2.1.6. Tea drinking

The results of the studies evaluating the effect of tea consumption on bladder cancer are also inconsistent. In 1991, the IARC working group concluded that there was inadequate evidence for the carcinogenicity of tea consumption in humans.[40] A recent meta-analysis has not found any association between tea consumption and bladder cancer.[36] The adjusted summary ORs for current tea consumers compared to non-drinkers was 1.08 (95%CI: 0.94, 1.24) for 7 studies with men, 0.99 (95%CI: 0.81, 1.20) for 6 studies with women and 1.01 (95%CI: 0.92, 1.10) for 7 studies with men and women combined.

2.1.7. Artificial sweeteners

Cyclamate was banned in 1970 from all dietary foods and fruits in the USA by the Food and Drug Administration because of induced cancer in experimental animals.[41] The European Union and the World Health Organization concluded in later research that cyclamate is not a carcinogen and readmitted it to the food market.[42] Besides cyclamate there are other artificial sweeteners on the market in the UK; saccharin, stevioside, thaumatin, aspartame, and acesulfame-k.[43] In 1999, the IARC evaluated the effect of saccharin and its salts on bladder cancer. The working group's conclusion was that these substances were not classifiable as carcinogenic in humans, despite there being sufficient evidence for the carcinogenicity of sodium saccharin in experimental animals.[44]

2.1.8. Medication

Phenacetin

The use of phenacetin-containing analgesics has been associated with an increased risk of renal pelvis TCC's. An association with bladder cancer has been found in most, but not all, published case-control studies.[45-47] In 1987, the IARC included phenacetin in Group 2A (probably carcinogenic to humans) and the analgesic mixtures containing phenacetin in Group 1 (human carcinogens). [48]

Paracetamol

In contrast, acetaminophen (paracetamol), the major metabolite of phenacetin, has generally not been found to increase the risk of bladder cancer [47;49-50]. Only the case-control study conducted by Steineck et al (1995) found a significant risk increase for TCC among users of paracetamol (OR=1.6; 95%CI: 1.1, 2.3). [51] However, analyses by duration and quantity of paracetamol use did not support this association. In 1999, the IARC concluded that there was

inadequate evidence for both humans and experimental animals as to the carcinogenicity of paracetamol. [52] Subsequent publications have also failed to demonstrate an association with bladder cancer risk.[45-46;53-54]

NSAID's

Regarding the use of non-steroidal anti-inflammatory drugs (NSAIDs), the intake of any class of NSAIDs, except for pyrazolone derivatives, was inversely associated with bladder cancer.[46] The protective effect was strongest among regular users of acetic acid compounds (OR=0.54; 95%CI: 0.31, 0.94) and weaker for users of aspirin, other salicylic acids and oxicams. However, other studies did not find any significant effect of NSAIDs on bladder cancer risk. [45;53;55-57]

Cyclophosphamide

Cyclophosphamide use has been found to be associated with an increased risk of bladder neoplasms [58-60] and it is also included in the group of human carcinogens.[48]

2.1.9. Occupational Exposures

Exposure to specific chemical carcinogens is another well-established risk factor for bladder cancer. Exposure to aromatic amines is associated with bladder cancer.[48] An excess risk of bladder cancer was also reported for dyers in textile industries, painters, varnishers and hairdressers.[61]

Other agents that have been associated with bladder cancer include polycyclic aromatic hydrocarbons (PAHs), used in aluminium production, coal gasification, coal tars, roofing and carbon black manufacture.[62] An excess risk in bladder cancer was reported among workers exposed to diesel engine exhaust, such as drivers. In a meta-analysis, the summary relative risk among truck-drivers was 1.17 (95%CI: 1.06, 1.29) and among bus drivers, it was 1.33 (95%CI: 1.22, 1.45).[63] High-risk occupations may account for 5-10% of bladder cancer cases in European men.[64]

2.1.10. Environmental exposures

Contaminants in drinking water

Several studies have found a positive association between chlorination by-products in drinking water and bladder cancer.[65-69] Some studies have found increased bladder cancer risks associated with exposure to high-levels of arsenic in drinking water.[70-73] An IARC working group has evaluated and classified arsenic in drinking water as carcinogenic to humans.[74] The data on exposure to nitrate in drinking water is limited and inconsistent.[67;75]

2.1.11. Radiation

Chronic low-dose radiation could affect bladder urothelium through oxidative stress and impairment of DNA repair. Therapeutic pelvic radiation, used for dysfunctional uterine bleeding and ovarian, cervical and prostate cancer is associated with an increase in bladder cancer risk.[76-79] Radioiodine (iodine-131), used for treating hyperthyroidism, was reported as being associated with bladder cancer in some, [80-81] but not all, publications.[82]

2.1.12. Urine pH

Rothman et al found that low urine pH was associated with elevated levels of free urinary benzidine and N-acetylbenzidine and 10-fold higher DNA adduct levels in exfoliated urothelial cells.[83] However, a recent case-control study did not detect an association between urine pH and bladder cancer.[84]

2.1.13. Menstrual, reproductive, and hormonal factors

Hormonal factors have been proposed as one explanation for the excessive incidence of bladder cancer in men.[85] Nevertheless, data on hormonal, menstrual, and reproductive factors and bladder cancer risk are scarce. A case-control study reported a decreased risk for ever-parous women who never-smoked (adjusted OR=0.51; 95%CI: 0.30, 0.88) and no apparent effect among ever smokers.[86] A more recent case-control study has not confirmed this association and has not found significant results for other menstrual and reproductive factors.[87] However, an elevated risk of bladder cancer for ever users of menopause hormone replacement therapy was observed (adjusted OR=3.29; 95%CI: 1.49, 7.25).[87]

2.1.14. Familial history of bladder cancer

Familial clustering of bladder cancer has been described in several case-reports.[88-91] The largest case-control study, including 2,982 bladder cancer patients and 5,782 controls, reported a statistically significant risk of bladder cancer for those with family history of genitourinary cancer (OR=1.45, 95%CI:1.2, 1.8).[92] The risk appeared to be higher among patients under age 45 (OR=2.7, 95%CI: 0.8, 8.9) and among women (OR=1.8, 95%CI: 1.1, 2.7).[92]

2.1.15. Hair dyes

The risk of bladder cancer associated with personal use of hair dyes is uncertain. Two cohort studies and several case-control studies have not observed any effect of permanent hair dye use and bladder cancer incidence or mortality. [93-98] Several other cohort and case-control studies have found an increased risk of bladder cancer among hairdressers and barbers who

are occupationally exposed to hair dyes.[99] Combined, these cohort studies give an estimated relative risk for bladder cancer associated with occupational exposure to hair dyes of 1.4 (183 observed vs 129 expected) based on 81,075 subjects (RR=1.1 for females and RR=1.6 for males).[99] A recent case-control study also reported an elevated risk of bladder cancer for women with frequent and long-term permanent dye use.[100] However, the carcinogenic risk associated with personal use of hair dyes remains unclear.

2.2. Objective

To examine if common and potentially modifiable dietary, lifestyle and environmental exposures affect the risk of recurrence and progression in bladder cancer.

2.3. Research Questions

2.3.1. Primary research questions

The following primary research questions have been selected on the basis of the strength of available evidence. They are also potentially amenable to modification by behavioural and lifestyle changes.

1. Among patients who are cigarette smokers at diagnosis, is stopping smoking associated with a lower risk of recurrence or progression compared to those who continue?
2. Is total fluid intake associated with the risk of recurrence or progression?
3. Is total fruit consumption associated with the risk of recurrence or progression?
4. Is toenail selenium level associated with the risk of recurrence or progression?

N.B. The effects of selenium and Vitamin E dietary supplementation will be investigated by a linked prospective randomised control trial “SELENIB” (Project A2). The trial will involve patients with histologically diagnosed TCC drawn from the study cohort and will require an additional informed consent procedure.

Due to the distinct disease characteristics and natural histories of non-muscle-invasive and muscle-invasive bladder cancer, it is imperative to examine these subgroups separately in relation to the above research questions. However a subgroup analysis of muscle invasive bladder cancer would lack power due to the relatively small number of cases. Therefore the focus of this study will be on patient with non-muscle-invasive bladder cancer, whilst collecting valuable information on patients with muscle-invasive disease.

2.3.2. Exploratory research questions

Are other putative risk factors for bladder cancer associated with bladder cancer recurrence or progression? These factors include:

- Smoking (Active and Passive)
- Diet (including vitamins and minerals)
- Types of beverages
- Medications
- Hair Dye
- Urine pH
- Artificial Sweeteners
- Medical history
- Menstrual and reproductive factors
- Family history of cancer
- Residential and occupational histories as proxies for environmental exposures.

2.4. Methods

2.4.1. Study design

Prospective Cohort Study

2.4.2. Setting

Urology centres in the West Midlands are invited to participate in The BCPP. The following Urology centres are located within the West Midlands:

- Arden Cancer Network
  - George Eliot Hospital NHS Trust
  - South Warwickshire General Hospitals NHS Trust
  - University Hospitals of Coventry and Warwickshire NHS Trust
  - Worcestershire Acute NHS Trust
- Black Country Cancer Network
  - Dudley Group of Hospitals NHS Trust
  - Royal Wolverhampton Hospitals NHS Trust
  - Walsall Hospitals NHS Trusts
- North West Midlands Cancer Network
  - Mid Staffordshire General Hospitals NHS Trust
  - Shrewsbury and Telford Hospitals NHS Trust
  - University Hospital of North Staffordshire NHS Trust
- Derby-Burton Cancer Network
  - Burton Hospitals NHS Trust

- Pan Birmingham Cancer Network
    - Birmingham Heartlands and Solihull NHS Trust
    - Good Hope Hospital NHS Trust
    - Sandwell and West Birmingham NHS Trust
    - University Hospital Birmingham NHS Foundation Trust
- Three Counties Cancer Network
    - Hereford Hospitals NHS Trust

2.4.3. Study population

Post-cystoscopy patients with a bladder abnormality that is suspicious of bladder cancer presenting to participating urology centres in the UK's West Midlands health region.

2.4.4. Recruitment of the cohort

Based on the incidence of bladder cancer from previous years (derived from regional cancer registry data), it has been estimated that approximately 4220 new cases of bladder cancer will be registered in the West Midlands during a 3 year study period, of which around 80% (3400) will meet the inclusion criteria for the study. It is expected that 1600 cases of non-muscle invasive TCC will be included in the primary analysis.

2.4.5. Inclusion / Exclusion Criteria

Inclusion Criteria

- Disease characteristics – Bladder lesion with with cytological evidence of high grade malignant cells, cystoscopic or imaging characteristics compatible with urothelial cancer/TCC or an incidental finding at rigid cystoscopy
- Able to give informed consent
- Age – 18 years or above
- Gender – both
- Fit for cystoscopy and surgical biopsy/resection

Exclusion criteria

- Previous diagnosis of cancer of the urethra, bladder, ureter or renal pelvis within the 10 years prior to current diagnosis
- Diagnosed of HIV infection
- Any condition which, in the opinion of the local investigator, might interfere with the safety of the patient or evaluation of the study objectives

All patients presenting with suspected urothelial cancer will be screened for entry into the cohort, subject to satisfying all other inclusion / exclusion criteria. **Primary analyses in**

Project A1 will however focus on patients with histologically proven urothelial cancer meeting one of the following criteria:

- **Stage Ta (any grade)**
- **Stage T1 (any grade)**
- **Stage Tis**

2.4.6. Patient identification, recruitment and consent process

Potentially eligible patients will usually be identified during haematuria clinics on the basis of abnormal cystoscopic findings suggestive of bladder cancer. However where flexible cystoscopy is not performed, patients may be considered for inclusion based upon cytological evidence of high grade malignant cells, imaging characteristics compatible with urothelial cancer/TCC or an incidental finding at rigid cystoscopy. Patient information sheets (see APPENDIX 1) will be given to eligible patients and patients will be given time to decide whether they wish to participate. The patient's written informed consent will be obtained before staging TURBT.

2.5. Data collection

Detailed information will be collected about the patients' lifestyle and their exposure to risk factors associated with bladder cancer using semi-structured questionnaires. A baseline questionnaire will be administered at the time of diagnosis. Further questionnaires will be administered to coincide with follow-up visits to capture information relating to changes in exposure.

A postal questionnaire will be used to collect historical information that may require the patient to check records or consult family or friends. Patients will also be asked to keep a 1 week food, fluid and micturition diary.

2.5.1. Baseline data collection

A semi-structured questionnaire (see APPENDIX 3) will be used to collect baseline data. This will be administered just prior to or just post TURBT.

The following information will be collected:

- Socio-demographic data – age, sex, ethnicity, marital status, education
- Environmental exposures - smoking, passive smoking, use of hair dye
- Medical history and use of medications
- Dietary intake – food type frequency, alcohol, caffeine and total fluid intake, use of vitamins and artificial sweeteners

- Health related quality of life (general questions for cancer patients)
- Social support

In addition, clinical data (tumour histopathology and treatment data) will be collected on case report forms (CRF's) from the patient's medical records. Biological samples will be collected at baseline: these include samples of tumour tissue, blood, and urine. Toenail samples may also be obtained for selenium level determination.

2.5.2. Postal questionnaire and diary

Prior to the first routine follow-up, patients will be sent a questionnaire to self complete. This questionnaire will collect data on patients' occupational history, residential history, family history of cancer and a 1-week food, fluid and micturition diary (See APPENDIX 3). Patients will be asked to either post back the completed questionnaire and diary in a pre-paid envelope or bring them back to the hospital when they attend for their first follow-up appointment.

2.5.3. Follow-up

The disease status of patients' participating in the study will be actively monitored for five years post-operatively via routine clinical follow-up visits. Thereafter, patients will be followed-up for mortality outcomes until 2025 via national registries (such as PHE Birmingham, formerly The West Midlands Cancer Intelligence Unit). Changes to exposure levels will also be documented using a follow-up questionnaire. The follow-up questionnaires will be undertaken at the initial post TURBT reassessment (e.g. approximately 3 months) and at each subsequent annual follow-up.

2.5.3.1. Post TURBT and annual follow-up data collection

The following re-assessment information will be collected at the initial post TURBT reassessment and then annually thereafter until the patient reaches the end of active monitoring at year 5.

- Follow-up CRF – disease status, details of recurrence or progression if appropriate
- Follow-up questionnaire:
    - Dietary intake – Food type frequency, alcohol, caffeine and total fluid intake, use of vitamins and artificial sweeteners
    - Changes in smoking habits and use of hair dye, vitamin supplements and artificial sweeteners
    - Changes to medical history or medications
    - Health related quality of life (general cancer and bladder cancer specific questions)

- Social support
- Utility based patient preference for regular surveillance

2.5.4. Follow-up after recurrence or progression

Additional information will be collected following recurrence. This will include pathological data, treatment details and status surveillance. Tumour tissue and blood serum samples will also be collected at resection where possible. Follow-up questionnaire data will continue to be collected following recurrence or progression. However the utility based patient preference for regular surveillance section will be omitted.

2.5.5. Central pathological review

In order to obtain standardised pathological data, 10% of all diagnostic haematoxylin and eosin stained slides will be reviewed centrally (see 5.3.3.3 for further details). The central review will reduce the bias caused by inter-reporter variability. The data generated by the central pathological review will not be used for any auditing purposes, but purely as a measure of consistency.

2.6. Statistical considerations

2.6.1. Primary Outcomes

Recurrence

Defined as the new occurrence of a bladder cancer at the same or different site as the initial index primary cancer and *excluding* recurrences identified at the first check cystoscopy.

Progression

Progression is defined as a RECURRENCE with:

- an increase in grade from grade 1/grade 2 to grade 3, or
- an increase in T-stage (determined by histopathology), or
- the new occurrence of carcinoma in situ (CIS) in a bladder previously free from CIS, or
- the new occurrence of multiple urothelial tumours following the initial diagnosis of a solitary urothelial tumour

OR:

- the need for a cystectomy because of refractory disease.

OR:

- the new development of nodal and/or distant metastases (determined by imaging)

2.6.2. Main statistical analysis

The main analysis for project A1 will focus on patients with non-muscle-invasive bladder cancer. Incidence rate ratios and corresponding 95% confidence intervals for recurrence and progression comparing high versus low levels of exposure for each of the exploratory variables (see 2.3.2) will be estimated by using age-adjusted and multivariable Cox proportional hazards model [102] processed with the Stata statistical software package. [103] The multivariable model will consist of covariates selected by hierarchical top-down evaluation of potential confounders but will include at least age, sex and cigarette smoking. The proportional hazards assumption will be tested using the scaled Schoenfeld residuals. [104]

Tests for dose-response trends in risk of recurrence or progression will be assessed by fitting ordinal exposure level variables as continuous terms. Statistical tests for interaction will be based on Wald statistics.[105] Two-sided p-values will be used throughout the project. A significance level of 0.05 will be used in all analyses.

2.6.3. Sample size and statistical power

Stopping smoking

Out of the cohort of 1,600 patients with non muscle invasive bladder cancer, we conservatively estimate that there would be about 720 current smokers at diagnosis available for this analysis. There is no reliable data on the proportion of patients who would stop smoking after a bladder cancer diagnosis but using information from studies on patients after myocardial infarction as a guide[106], we assume that 30% of smokers would have become non-smokers by the first anniversary. We further assume five-year recurrence and progression rates among those who continue to smoke to be 45% and 23% respectively, and 5% loss to follow up. With a sample of 720, we would be able to detect rate ratios of ≤ 0.66 for recurrence and ≤ 0.54 for progression (80% power, 2-sided $\alpha = 0.05$), comparing those who stop to those who continue. The power would be higher if there are more smokers in the cohort at baseline.

Fluid and fruit consumption and toenail selenium

Power calculation is based on the non-muscle invasive cohort. For comparison between two equal-sized groups, we again assume five-year recurrence and progression rates in those with below median consumptions to be 45% and 23% respectively, and 5% loss to follow up. With 1,600 non-muscle invasive patients, we would be able to detect rate ratios of ≤ 0.78 for recurrence and ≤ 0.70 for progression (above vs below median; 80% power, 2-sided $\alpha = 0.05$). Powers would be considerably higher if these exposures were analysed as continuous variables.

SECTION 3: PROJECT A2: *'SELENIB'* TRIAL

The use of selenium and vitamin E supplementation to prevent recurrence and progression of non-muscle-invasive bladder cancer

3.1. Trial Summary

The SELENIB trial is a randomised double-blinded placebo-controlled trial which will recruit patients with histologically confirmed transitional cell carcinoma (TCC) of the bladder from within the BCPP cohort. The SELENIB trial will examine the effect of selenium and vitamin E (d-α-tocopherol) supplementation on recurrence and progression amongst patients with bladder TCC.

Patients newly diagnosed with non-muscle-invasive TCCs will be randomised following their staging TURBT in a 2x2 factorial design. They will receive daily supplementation with selenium or placebo and vitamin E or placebo for up to five years. Participants will be followed up by routine cystoscopic surveillance, the primary outcome measure being recurrence-free interval. It is anticipated that 515 patients will be randomised over three years in Urology centres across the West Midlands.

3.2. Background

3.2.1. Evidence to justify the choice of interventions tested - selenium

3.2.1.1. Laboratory studies

A large body of experimental laboratory work exists to support the role of selenium in reducing the risk of cancer.[108-110] Selenium compounds may act as essential components of antioxidant enzymes scavenging DNA-damaging oxygen free radicals.[111] Selenium may also activate the DNA repair branch of the p53 pathway,[112] and it has been shown to inhibit angiogenesis[113] and DNA cytosine methyltransferase.[114] In addition, it has effects on the binding of transcription factors to DNA[115] and acts as a potent inducer of apoptosis.[116]

In animal models, low levels of selenium-dependent glutathione peroxidase have been found to be responsible for the vulnerability of rabbit bladder urothelium to chemical carcinogenesis,[117] and it has been demonstrated that sodium selenite administration can reduce the occurrence of butylbutanolnitrosamine-induced bladder cancer in rats by over 40%.[118] Protective effects of selenium have also been shown in animal studies in other sites, including prostate, colon and lung.[108]

In summary, laboratory evidence suggests that selenium may be important in reducing the risk of transformation of the urothelium and in inhibiting disease progression following transformation.

3.2.1.2. Prospective cohort studies

Six prospective cohort studies have investigated the association between serum or toenail selenium levels and bladder cancer incidence.[24-29] Members of the BCPP Working Group previously reviewed the results from five of them.[31] In the largest of these studies, there was a significant inverse association between baseline selenium and subsequent bladder cancer risk. In this study, the rate ratio of bladder cancer incidence for the top vs bottom quintile of toenail selenium levels was 0.67 (95% CI 0.46-0.97), with a statistically significant linear trend over the five quintiles. This association was particularly strong in muscle-invasive tumours, indicating that low selenium levels might be associated with cancer progression. Apart from smoking, selenium was the only important environmental exposure identified to be significantly associated with bladder cancer risk in this large cohort study, thus strengthening the possibility that the relationship is causal on the grounds of specificity.[28] Of the other four studies,[24-27] three [24-26] reported reduction in risk associated with higher baseline selenium but their powers were limited by the relatively small number of cases (92 cases in total).

There is considerable evidence from observational studies to support the potential benefit of selenium against the risk of other cancers.[108] Examples of large, well-conducted cohort studies include prostate,[119] lung,[120] liver [121] and oesophagus [122] cancers. The findings on lung cancer are especially interesting because it shares a common aetiology with bladder cancer - cigarette smoking. In the case of prostate cancer, a number of studies have shown a greater protective effect of selenium against advanced disease than localised disease, suggesting that selenium can slow cancer progression.[119;123-125]

3.2.1.3. Intervention studies

No controlled trials testing the effect of selenium in bladder cancer incidence or recurrence have been conducted or are ongoing. However, there have been several trials with selenium as the sole intervention or in combination with other agents to assess the effect on other cancer endpoints.[126-128] These studies have reported statistically significant protective effects of selenium on all cause mortality,[126] total cancer mortality and incidence [127] and liver cancer mortality.[128] Unfortunately, none of the studies had bladder cancer as a pre-specified endpoint or had enough bladder cancer cases to examine the role of selenium in reducing risk. Of

interest is the trial of Clark et al, where, the strongest treatment effect was observed in subjects in the lowest tertile of plasma selenium at baseline,[129] a level similar to that found in the UK population.[130]

There are several ongoing trials assessing the chemopreventive effects of selenium in both primary and secondary prevention in a number of sites including incidence and progression of prostate cancer (SELECT),[107;131] recurrence in colorectal adenoma,[132] and in stage I non-small cell lung cancer.[133]

3.2.2. Evidence to justify the choice of interventions tested – Vitamin E

3.2.2.1. Laboratory studies

Vitamin E includes a group of tocopherols and tocotrienols, of which α-tocopherol has the highest biological activity.[134] As a group, vitamin E has been shown to be a strong antioxidant;[135-136] also inhibiting the formation of nitrosamines,[137] protein kinase C [138] and prostaglandin metabolism.[139] These properties suggest that this vitamin could have a role in reducing the risk of cancer.

Using an immortalized non-tumourigenic rat urothelial cell line (MYP3), Tamatani et al. examined the effect of lipopolysaccharide-activated polymorphonuclear leukocytes on malignant transformation and found that α-tocopherol reduced the number of colonies induced.[140] Similarly, in another model based on hydrogen peroxide induced transformation of a non-tumourigenic cell line, vitamin E reduced TNF-α stimulated colony growth.[141] Two studies using rats exposed to the carcinogen N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN) demonstrated that vitamin E administration resulted in a reduction in cellular atypia [142] and papillary or nodular hyperplasia of the urinary bladder.[143] The potential importance of vitamin E has also been supported by animal studies on chemically induced colonic,[144] breast [145] and oral [146] tumours.

3.2.2.2. Prospective cohort studies

The epidemiological association between vitamin E supplement use and bladder cancer has been examined in two large cohort studies in the US. In the Health Professionals Follow-up Study cohort, current use of vitamin E supplements was associated with a lower bladder cancer risk (RR = 0.70, 95% CI 0.52 – 0.96, for current vs never users).[32] In the Cancer Prevention Study II, regular vitamin E supplement use for 10 or more years was associated with a reduction in bladder cancer mortality among cigarette smokers (RR=0.60, 95% CI 0.37-0.96). Smaller, non-significant reductions in risk were observed among non-smokers.

To date, three prospective cohort studies have investigated the association between dietary vitamin E intake and bladder cancer.[32;147-148] The Health Professionals Follow-up Study [32] reported lower bladder cancer risk of highest versus lowest quintiles of intake (RR = 0.64, 95% CI 0.45-0.92); the effect was confined to α- but not γ-tocopherol. In an observational analysis of the Finnish ATBC trial, participants who were randomised to double placebos (for both β-carotene and α-tocopherol) had a borderline negative association between dietary intake and risk (RR = 0.49, 95% CI 0.22 – 1.07, for highest vs lowest quintiles; p for linear trend = 0.06).[147] The third study, the Netherlands Cohort Study, did not find any association, [148] although it did not report data on α-tocopherol alone, unlike the Health Professionals Follow-up Study.[32]

3.2.2.3. Intervention studies

There are two relevant trials. The ATBC trial in Finland found no association between vitamin E supplementation and bladder cancer incidence after a median of 6 years supplementation and follow-up (RR = 1.1, 95% CI 0.8-1.5).[149] However, this trial used a low dose of vitamin E (50 IU/day), only included male smokers, and was under-powered. We have estimated that with 169 cases of bladder cancer, the study had less than 70% power to detect a relative risk reduction as large as 40% (RR ≤ 0.6), and less than 45% power if the benefit was 30% (RR ≤ 0.7).

A study more directly relevant to the question of risk of recurrence was reported by Lamm et al.[150] In this small trial, they randomised 65 patients with superficial bladder tumours to either multiple vitamins at the recommended daily allowance (RDA) or RDA plus high doses of vitamin E (400 IU/day), vitamin A (40,000 IU/day), vitamin C (2,000 mg/day), and vitamin B6 (100 mg/day). Overall recurrence rates were 24/30 (80%) in the RDA group and 14/35 (40%) in the high dose group (two tailed Fisher's exact test p = 0.0011).[150] Although the study was small, the observed benefit was remarkable enough to warrant verification by a large trial. However, there are concerns for the toxicity of vitamin A,[151] and there is inadequate evidence supporting the use of vitamin C (reviewed in reference 31). Furthermore, there is direct evidence of ineffectiveness from previous phase III trials concerning vitamin B6 [152] and synthetic forms of vitamin A.[153]

This evidence suggests that vitamin E was most likely to have been responsible for the observed benefit.

Of the recent trials on other chemopreventive agents in patients with non-muscle-invasive TCCs, there are four phase III trials that are ongoing or have recently finished.[154] The agents being tested include DFMO (an antiproliferative agent), 4HPR (a retinoid), celecoxib (a COX-2 inhibitor) and megadoses of multivitamins. A preliminary announcement on the findings of DFMO has been made, reporting no benefit on the risk of recurrence.[155] The statistical power of all of these studies could be limited by their sample sizes (ranging from 160 to 360) and duration of treatment (one to three years). However, in parallel with the SELENIB trial, a large British trial using a Cox-2 inhibitor is currently in the planning phase

3.2.3. Significance of the SELENIB trial

There is mechanistic evidence suggesting that selenium may reduce the risk of recurrence and progression of TCCs. In addition to the supportive findings from three smaller cohorts, the largest prospective study [28] to date examining selenium and bladder cancer risk showed that low selenium intake may be associated with progression of TCCs. The aggregate evidence from cohort studies and controlled trials on other cancer sites also suggest that selenium has potentially important chemopreventive effects. The significance of this trial is further highlighted by two other facts: firstly, the population dietary selenium intake in the UK is relatively low by international standards and is declining.[130] There would thus be large scope for modification if the protective effect of selenium is confirmed. Secondly, selenium supplements are inexpensive, simple and non-toxic, distinguishing them from other pharmaceutical agents with chemopreventive potential.

The addition of vitamin E as a second factor is allowing us to test an additional hypothesis. The enthusiasm for vitamin E has been dampened considerably following reports on the lack of protection against cardiovascular diseases [156] and lung cancer.[157] However, there remains a strong case in examining its chemopreventive potential in bladder cancer patients. As in the case of selenium, vitamin E has large primary prevention potential because of its presence in the diet, in contrast to many other potential candidates.

It is postulated that selenium and vitamin E could act synergistically in inhibiting carcinogenesis.[158] However, results from the large Netherlands Cohort Study provide a strong indication that substantial interaction is unlikely in the case of bladder cancer.[28] In our 2x2 factorial design we are able to address two hypotheses with the same number of patients and it is not our intention to formally test any interaction between the two agents (see 3.9.3 on implications on power calculation).

3.3. Objective

To investigate whether selenium and/or vitamin E (α-tocopherol) supplementation reduces the risk of recurrence and progression in patients with non-muscle-invasive bladder cancer.

3.4. Methods

3.4.1. Trial design

Double-blinded, placebo-controlled, 2x2 factorial randomised controlled trial

3.4.2. Trial population

Patients with pathologically confirmed non-muscle-invasive TCC of the bladder.

It is anticipated that the majority of the eligible patients for SELENIB will previously have been recruited into the BCPP Cohort (see below). However patients not in the BCPP cohort and otherwise eligible can also be included.

3.4.3. Patient recruitment

The Bladder Cancer Prognosis Programme aims to recruit patients newly-diagnosed with bladder cancer in the West Midlands. We estimate that 1,600 of these patients will be diagnosed with non-muscle-invasive bladder cancer during the recruitment period of the programme. This latter subgroup will be screened according to the inclusion/exclusion criteria for SELENIB, and it is anticipated that 515 eligible patients will be randomised into the SELENIB trial.

The anticipated randomisation rate is based upon a pilot study, in which Rayman et al randomised the same proportion of eligible and screened individuals in a target population of healthy men and women invited by general practices.[130] Cancer patients as a group are motivated to achieve the best response from various modalities of treatments offered, and chemoprevention using simple and non-toxic nutritional supplementation is likely to be highly acceptable to them. It is therefore anticipated that the SELENIB trial will achieve at least a similar uptake rate among patients recently diagnosed with TCCs. The very rapid recruitment in the ongoing SELECT trial [107] (using similar treatments in healthy men in the US) is also encouraging.

It is anticipated that the loss to follow-up will be in the region of 5% as patients will all be under routine clinical surveillance.

3.4.4. Eligibility criteria

3.4.4.1. Inclusion criteria

- Able to give informed consent for SELENIB
- Able to be randomised within twelve months of diagnostic TURBT/biopsy (usually at the first routine visit to hospital after diagnosis)
- An initial diagnosis of:
  - Histopathologically confirmed non-muscle-invasive transitional cell carcinoma (<pT2) (i.e. All stage pTa, pT1 or pTcis)

3.4.4.2. Exclusion criteria

- Disease characteristics of stage pT2 and above
- Patients who are pregnant or breastfeeding
- Patients diagnosed with HIV infection
- Patients who are on immunosuppressive therapy following organ transplantation
- Patients taking cyclosporin
- Any condition which, in the opinion of the local investigator, might interfere with the safety of the patient or evaluation of the trial objectives.

Patients who currently use or have used selenium and/or vitamin E supplements would **not** be excluded. However, they must agree not to take supplements containing more than 200mcg selenium and 100IU vitamin E per day apart from the trial medication.

3.4.5. Patient identification, recruitment and consent process

Following TURBT patients clinically suspected of having non-muscle-invasive bladder cancer will be given an information leaflet. Following pathological diagnosis, eligible patients will be given additional information as required and invited to return to hospital to discuss the SELENIB trial further. After obtaining written informed consent, the patient will be randomised.

It has been deemed necessary for SELENIB patients to be re-consented for their long-term follow-up after they have completed taking their trial medication (see Addendum 1.0 to patient information sheet, November 2011). Where possible, this re-consent process will be carried out in person. However, where this is not feasible within a realistic timeframe, patients will be contacted by telephone to inform them of the need for this re-consent. The re-consent form will then be sent to the patient by post, which they will complete and return to the site by post.

3.4.6. Randomisation

3.4.6.1. Stratification

Randomisation will be stratified by recurrence risk group (high versus intermediate) and treatment centre. The method of random permuted blocks will be used to ensure balance within each strata defined by recurrence risk group and a minimisation approach will be used to balance treatments within centres.

Table 1: EAU Risk Groups

Low risk	Intermediate Risk	High Risk
• Solitary G1 pTa <3cm	• Multiple G1 pTa (>1) • Solitary G1 pTa ≥3cm • G2 pTa • G1 pT1 • G2 pT1 (1 or 2 tumours)	• G3 pTa • G3 pT1 • CIS • Multiple G2 pT1 (3 or more foci)

Table 2: EAU Stage and Grade Risk Group Matrix

STAGE GRADE	pTa	pT1	pTcis
G1	<3cm Low Risk ≥3cm Intermediate Risk	Intermediate Risk	High Risk
G2	Intermediate Risk	<3 Intermediate Risk ≥3 High Risk	High Risk
G3	High Risk	High Risk	High Risk

Patients will be allocated to a recurrence risk group based on local pathological diagnosis. Recurrence risk groups will be designated according to the European Association of Urologists (EAU) guidelines on bladder cancer.[160]

3.4.6.2. Allocation of Treatment

Prior to the launch of the trial, a list of Treatment Pack Numbers will be generated. A computer will be used to randomly assign each Treatment Pack Number to one of the four treatment arms (labelled as A, B, C or D). The treatments will be allocated using the random permuted blocks method. Each block will consist of 4 Treatment Pack Numbers (1 number randomly allocated to each of the four treatment arms).

Once a patient is deemed to be eligible for the trial and has given written informed consent, a member of our research team will randomise the patient either by using the online database or

by phoning the Study Office at the University of Birmingham. A computerised algorithm will randomly allocate the patient to a treatment arm according to their risk strata and treatment centre. **The allocated treatment arm will not be revealed**. The computer will select the next available Treatment (Pack) Number that corresponds with the allocated treatment arm from the available Treatment (Pack) Numbers in stock within the study site. The Treatment Pack Number will remain a unique number for that patient for the duration of the trial. A unique Trial Number will also be allocated.

At randomisation and at six monthly follow-up visits, patients will be given a Treatment 'Pack'. Each Pack will comprise one box containing a six month supply of selenium/placebo tablets and one box containing a six month supply of vitamin E/placebo gel capsules. Both boxes will be labelled prior to distribution. These labels will display the Treatment Pack Number.

3.4.6.3. Blinding

The allocation of treatments will be blinded to ensure that neither the patient nor the clinical, pharmacy or research personnel are aware of the outcome of the randomisation. For details of the unblinding procedure please refer to section 3.5.2.6.

3.5. Investigational Medicinal Product (IMP)

The two active interventions are selenium (200 mcg/day, in the form of high-selenium yeast, SelenoPreciseTM) and vitamin E (200 IU/day in the form of natural d-α-tocopherol, equivalent to 154 mg/day).

Participants will be randomised to one of the following four treatment arms:

- Selenium tablet + vitamin E capsule
- Selenium tablet + placebo capsule
- Placebo tablet + vitamin E capsule
- Placebo tablet + placebo capsule

Each arm consists of a tablet (selenium or placebo) and a soft gel capsule (vitamin E or placebo). Placebos will be manufactured to be identical in appearance, smell and taste to the active agents. They will be identical in their composition except for the active ingredient (See APPENDIX 5 for full treatment formulation details).

All study treatments will be manufactured, packed and released by:
Pharma Nord ApS, Tinglykke 4-6, 6500 Vojens, Denmark.

Pharma Nord Aps is authorised by the Danish National Food Agency to produce food and food supplements and by the Danish Medicines Agency (DKMA) to produce medicinal products.

3.5.1. Justification for dosages

3.5.1.1. Selenium

The daily dosage of 200mcg of selenium to be used in the SELENIB trial is identical to those used in previous trials by Clark et al.[127] and Yu et al.[128] (who reported benefits on total cancer and liver cancer mortality respectively) and the ongoing SELECT trial for prostate cancer prevention.[107] The safety of 100-200mcg daily selenium is well established. The tolerable upper intake level of selenium for adults is 400mcg daily.

3.5.1.2. Vitamin E

Previous cardiovascular prevention trials on vitamin E have used either the natural or the synthetic form.[156] The former is a single stereoisomer (RRR [2'R, 4'R, 8'R], or d-α-tocopherol, 1.5 IU/mg) while the latter is a mixture of eight stereoisomers (all-racemic or all-rac, 1.1 IU/mg).[159] We have chosen the naturally existing d-α-tocopherol, which also has higher bioavailability.[134] Vitamin E is well-tolerated even in high doses (above 400 IU daily).[161]

The SELENIB dose of 200 IU daily is well within the US Institute of Medicine Food and Nutrition Board's tolerable upper intake level of 1000mg or 1100 IU.[161] A recent meta-analysis of 135,967 patients from 19 trials (mean age 47 to 84 years, average follow-up 1.4 to 8.2 years) has raised some concerns over the long-term safety of doses over 400 IU, with a statistically significant increase in all-cause mortality (RR 1.04 (95% CI, 1.01 to 1.07).[162] However, this effect was not seen when doses below 400 IU were used.[162] In fact, it was noted that there may be a mortality benefit with low-dosage vitamin E supplementation (below 400 IU), this benefit being significant in 4-way analysis.[162]

The finding of an increased mortality risk from high-dosage vitamin E supplementation (above 400 IU) has been challenged [161] and the possible mechanism of this effect is unclear, although a number of causes and biological mechanisms have been proposed including disruption of antioxidant and coagulation mechanisms.[163] In the ATBC study vitamin E supplementation (50 IU daily) increased the risk for haemorrhagic stroke but significantly reduced the risk for ischaemic stroke, with an overall lower stroke rate in the group receiving vitamin E.[157] High intake of vitamin E may influence coagulation in some persons with drug-induced vitamin K deficiency but this effect does not seem to occur in persons with adequate amounts of vitamin K,[161] and a large trial of patients taking long-term warfarin who also took 800-1200mg vitamin

E daily showed no changes in coagulation variables that would suggest an increased risk of bleeding.[161] Despite the evidence suggesting caution with high-dosage vitamin E supplementation (above 400 IU daily), there appears to be an equal amount of evidence suggesting a benefit from low-dosage vitamin E supplementation and we therefore consider our dosing of 200 IU daily to be justified.

3.5.2. Drug administration

3.5.2.1. Dose schedule

Patients will be provided with an initial six-month supply of their allocated treatment at the time of randomisation. The ideal time to commence treatment will be on the same day as randomisation. The patient will be instructed to take one tablet (selenium/placebo) and one gel capsule (vitamin E/placebo) once daily with food for a period of up to 5 years. Patients will be re-supplied with treatments every six months throughout the duration of the treatment period.

3.5.2.2. Distribution

The trial treatments will be distributed periodically to the pharmacy department within each centre by Pharma Nord. Stock levels within each study site will be monitored. A centralised ordering process will ensure that unallocated treatment packs are replenished regularly and allocated 'repeat' packs arrive at the study site prior to patient follow-up.

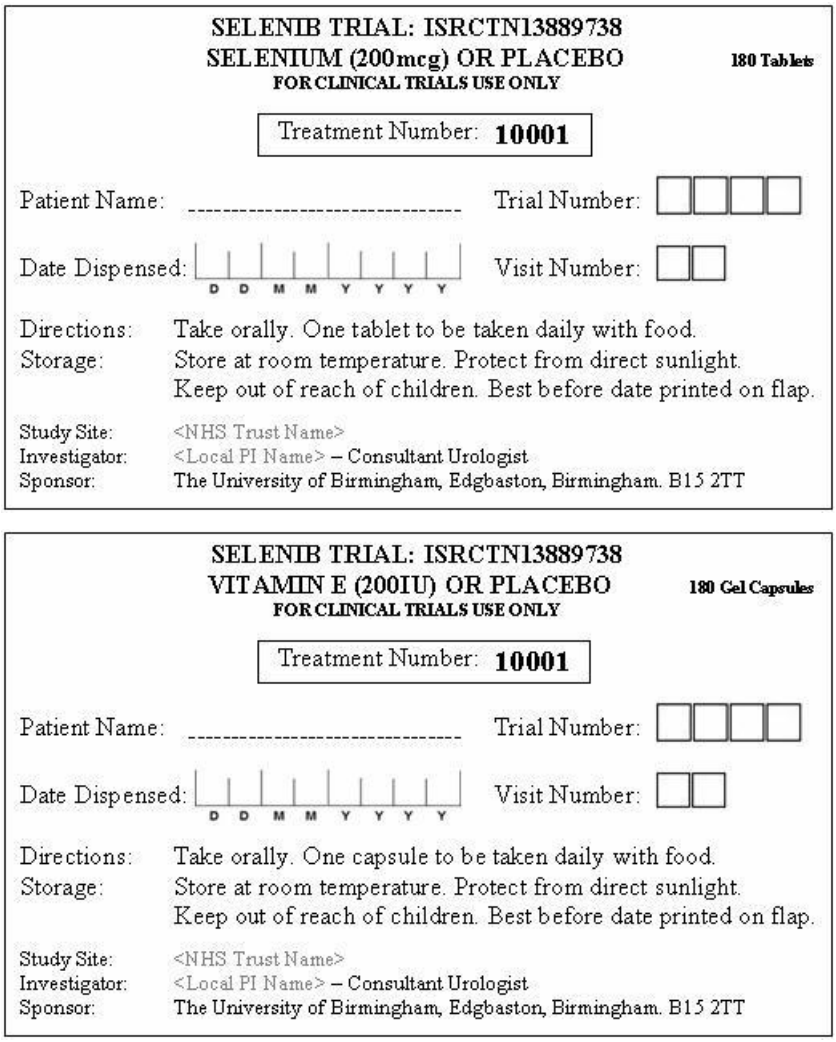
3.5.2.3. Packaging and labels

Selenium, vitamin E and identical placebos will be supplied in PVdC/PVC blister packs of 30 tablets/capsules with aluminium foil backing in a cardboard box. Each box will contain 180 tablets/capsules (6 blister packs). Labels will be attached to the box prior to distribution to pharmacies. The label will include;

- Unique Treatment (Pack) number
- Trial acronym ("SELENIB")
- Unique Trial Number (to be completed)
- Patient name (to be completed)
- Patient date of birth (to be completed)
- Visit number (to be completed)
- Storage and administration instructions
- Pharmaceutical dosage, form and route of administration
- Name of local investigator
- Name of study site
- Name and address of sponsor organisation

The contact details of the local pharmacy will also be given to the patient in the SELENIB Treatment Diary for the purposes of emergency un-blinding. Further information regarding the treatments will be provided in the SELENIB Treatment Diary (APPENDIX 4).

Figure 2: Example SELENIB Treatment Labels



3.5.2.4. Dispensing

Upon randomisation a prescription for the allocated Treatment Pack will be signed off by the Principal Investigator (or clinician designated by the Principal Investigator). The patient will be dispensed a Treatment Pack (1 box containing a six month supply of selenium or placebo and 1 box containing a six month supply of vitamin E or placebo) bearing the their corresponding Treatment Pack Number and visit number. Prior to dispensing the patients name, trial number and date of dispensing and visit number will be added to each treatment pack label. The dispensing of the trial treatment will be documented on the relevant paperwork at site.

3.5.2.5. Storage

Treatment Packs are to be kept at room temperature and protected from direct sunlight. The local investigator is responsible for ensuring that the study treatments are stored in an appropriate secure area prior to dispensing.

3.5.2.6. Code breaking

Un-blinding envelopes will be provided along with each delivery of initial treatment packs. The envelopes will be filed in a secure area of the pharmacy department. Un-blinding is restricted to emergency situations and should only be used under circumstances where knowledge of the treatment is essential for the clinical care of the patient. If the treatment code is broken, the reason and date should be recorded and signed by the local Principal Investigator. Access to the code break information should be restricted to pharmacy personnel only. All other site personnel should remain blinded.

3.5.2.7. Drug interactions / precautions

<u>Selenium</u>

There are no known contraindications, interactions or precautions for the use of selenium. Ingestion in doses above the No-Observed-Adverse-Effect level of 800mcg daily may induce hair and nail brittleness and loss. Other reported effects at lower doses include gastrointestinal disturbances, fatigue, garlic breath odour, and irritability.

<u>Vitamin E</u>

Large doses of vitamin E (above 400 IU daily) may cause diarrhoea, abdominal pain, and other gastrointestinal disturbances, and have also been reported to cause blurred vision, dizziness, fatigue and weakness.

Vitamin E may increase the effect of anticoagulant medication. However, the evidence for this is unclear (see section 3.5.1.2).

Cyclosporin absorption can be increased by Vitamin E. In one study of ten healthy subjects the AUC of cyclosporin increased by 60%, and it was suggested that the absorption was increased due to improved stabilisation and micelle formation within the gut or due to decreased intestinal metabolism.[164] **Patients on immunosuppressive therapy following**

organ transplantation are excluded from this study, as are patients who are taking cyclosporin for other indications.

Selenium plus Vitamin E

Although no previously completed studies have evaluated selenium and vitamin E together, the combination of these supplements is not expected to cause extra side effects. A large trial (SELECT) involving over 30,000 healthy American men, using this combination is currently ongoing to test it's effectiveness in preventing prostate cancer.[107] To date we are not aware of any published reports of significant adverse events from this trial.

Pregnancy

Pregnancy is an exclusion criteria for this study. However, there are many studies investigating the potential benefits of selenium supplementation in preventing a range of neonatal conditions, and safety during pregnancy has not been questioned. There is currently no information available to assess any benefits or harms of supplementing women during pregnancy with vitamin E.[165]

3.5.2.8. Compliance and drug accountability

The importance of compliance will be explained to the patient at recruitment. A member of our research team will telephone the patients monthly during the first three months of treatment to reinforce this message and at each 6-monthly follow-up throughout the duration of the study. Every effort will be made to encourage patients to return the unused medication and empty packs. Our researcher will count and record the number of used and unused tablets/capsules. The unused medication will be collected and destroyed by pharmacy. Patients will be asked to mark off in the SELENIB Treatment Diary provided, each day that they have taken or missed their study treatment. This diary will be examined during the follow-up appointment.

Blood serum vitamin E and toenail selenium levels may be checked in a random sample of patients to verify correct treatment allocation and compliance.

Patients who currently use or have used selenium and/or vitamin E supplements would **not** be excluded. However, they must agree not to take supplements containing more than 200mcg selenium and 100IU vitamin E per day apart from the trial medication.

3.6. Data Collection

3.6.1. Trial evaluations

Patients will be invited to attend a SELENIB follow-up clinic every 6 months for up to five years following randomisation. At each follow-up, treatment compliance, toxicity and disease status data will be recorded by our researcher.

Patients who are taking anticoagulant medication should have their blood clotting checked at their anticoagulation clinic at 1 week, 2 weeks, and 4 weeks after commencing trial medication. At the time of randomisation the anticoagulation clinic will be notified of this requirement by telephone call and letter, and the patient's General Practitioner will be notified by letter.

3.7. Adverse Events / Serious Adverse Events

For the purpose of this trial, any detrimental change in the patient's condition subsequent to the start of trial treatment and during the trial follow-up period, which is not unequivocally due to the underlying disease process of bladder cancer, should be considered as either an adverse event (AE) or a serious adverse event (SAE).

3.7.1. Definition of an Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An unexpected adverse event is one that is not listed as a known toxicity of the investigational drug in the summary of product characteristics.

3.7.2. Serious Adverse Event (SAE)

3.7.2.1. SAE Definition

Serious unexpected adverse events include any untoward medical occurrence that;

- results in death*;
- is life threatening;
- requires in-patient hospitalisation or prolongation of existing hospitalisation**;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

* Any death, irrespective of cause, is considered as a serious adverse event.
** In-patient hospitalisation or prolongation of existing hospitalisation required for routine treatment of bladder cancer should not be reported as an SAE. Any other toxicity which is serious enough to require inpatient hospitalisation should be reported as an SAE.

3.7.2.2. AE and SAE Monitoring Strategy

Adverse events will be monitored during regular SELENIB follow-up visits. Our researcher will complete an Adverse Event checklist (APPENDIX 6) with the patient to ensure that any adverse events that have occurred between follow-ups are documented. Patients will be provided with a treatment diary containing information about known side effects of the active treatments. This diary will also contain our researcher's contact telephone number. Patients will be asked to keep this diary in a safe place to be retained throughout the duration of the treatment. A copy of the SELENIB patient information leaflet will also be sent to the patients GP.

The patient will be instructed to notify our researcher by telephone immediately following any event meeting the above SAE classifications.

Due to the relative safety of the treatments used in the SELENIB trial, there are no additional on-treatment investigations required for the monitoring of Serious Adverse Events or treatment related toxicities, other than for patients taking anti-coagulation medication (as described above in section 3.5.1.2).

3.7.2.3. SAE Reporting Requirements - Study Site

An event suspected to be an SAE must be reported immediately upon knowledge of the event to the BCPP Study Office (within a maximum of 24 hours). SAEs must be reported in this manner for the duration of the study and up to 28 days after cessation of trial treatment. The SAE form must be submitted by fax along with any supporting information. In circumstances where supporting information is not immediately available, the SAE form must be submitted to the Study Office immediately and followed-up by a complete report within a further 4 calendar days. It is essential that the person reporting the SAE gives as much information as possible, including an assessment of seriousness and causality.

The Principal Investigator (or person designated by the Principal Investigator) will assess whether the SAE is related or unrelated to the trial treatment (defined in Table 3 below as

unrelated, unlikely, possible, probable, definitely, and not assessable) and that assessment will be recorded on the SAE form.

Table 3: SAE Causality Definitions

Relationship	Description
UNRELATED	There is no evidence of any causal relationship.
UNLIKELY	There is little evidence to suggest a causal relationship or there is another reasonable explanation for the event (e.g. the patients' clinical condition, other concomitant treatments).
POSSIBLE	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the patients' 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.

The SAE form must be signed by the Principal Investigator (or person designated by the Principal Investigator). A full audit trail must be maintained in the centre to document the reporting of the SAE.

3.7.2.4. SAE Reporting Requirements –Study Office

All SAE Forms received in the Study Office must be reviewed by the Chief Investigator (or person designated by the Chief Investigator) who will classify the SAE into one of the following two categories:

- Suspected Unexpected Serious Adverse Reaction (SUSAR) (which may or may not be fatal and life threatening),
- Suspected Serious Adverse Reaction (SSAR)

For reporting purposes, rare but recognised complications of the underlying disease, or standard drugs used to treat it, will not be considered as 'unexpected'. The Chief Investigator is responsible for onward reporting of the event, as required by current legislation. A fully documented audit trial will be maintained both at the study site and at the Study Office.

If a reported SAE is considered a major cause of concern in relation to current or future patients on the trial, the Chief Investigator will issue an urgent safety notice to all protocol recipients, pending a formal protocol amendment. This notice will be sent out as a matter of urgency, and will contain a clear explanation of the event and any treatment recommendations.

A report of all SAE's (including non SUSAR events) will be submitted annually to MHRA and the main REC.

3.8. Study Drug Discontinuation

3.8.1. Discontinuation criteria

Patients will be instructed to immediately stop treatment in the event of:

- disease progression (as defined in section 3.9.1) OR
- any toxicity at grade 3 or above, which the local clinician deems attributable to the study treatment, OR
- any persistent toxicity, which the local clinician deems attributable to the study treatment and which the clinician or the patient feels warrants discontinuation, OR
- a request from the clinician for discontinuation of treatment for other reasons, OR
- a request from the patient for discontinuation of treatment OR
- Patient withdraws from the SELENIB trial (See section 7.7)

The primary endpoint for the SELENIB trial is recurrence free interval. It is plausible that the study treatments may reduce the recurrence rate without preventing it completely or prevent progression; hence patients will continue therapy following recurrence. Once a patient develops progressive disease, treatment will be discontinued as further benefit is unlikely.

3.8.2. Management of patients and study treatment

Participation in the SELENIB trial will not compromise any other treatment that is clinically indicated.

Subject to a patient discontinuing treatment or withdrawing from the trial clinical follow-up will continue as per local policy. The patient will not be required to attend subsequent SELENIB follow-up clinics. Follow-up data will continue to be collected until the end of the study, except for cases where the patient has specifically requested that no further follow-up data be collected.

Unused treatment packs will be collected and returned to pharmacy to be destroyed.

3.9. Statistical Considerations.

3.9.1. Outcome Measures

Primary Outcome Measure

- Recurrence-free interval

This is defined as time from date of trial entry to date of recurrence. For those patients who are not observed to have a recurrence by the time of analysis, the interval will be censored at date last known to be recurrence-free. A recurrence is defined as the new occurrence of a bladder cancer at the same or different site as the initial index primary cancer and *excluding* tumours identified at the first check cystoscopy.

Recurrence at the 3-month follow up cystoscopy will be excluded as the majority of these "recurrences" are predominantly due to incomplete resection of the primary index tumour, and have little prospect of being affected by any chemoprevention.

Secondary Outcome Measures

- Progression-free interval: this is defined as time from date of trial entry to date of progression. For those patients who are not observed to have a progression by the time of analysis, the interval will be censored at date last known to be progression-free. Our definition of progression includes important risk factors for "progression to muscle-invasive disease", a clinically important endpoint.

  Progression is defined as a RECURRENCE with:
  - an increase in grade from grade 1/grade 2 to grade 3, or
  - an increase in T-stage (determined by histopathology), or
  - the new occurrence of carcinoma in situ (CIS) in a bladder previously free from CIS, or
  - the new occurrence of multiple urothelial tumours following the initial diagnosis of a solitary urothelial tumour

  OR:
  - the need for a cystectomy because of refractory disease

  OR:
  - the new development of nodal and/or distant metastases (determined by imaging)

- Overall survival
- Incidence of all other clinically-diagnosed malignancies

- Incidence of cardiovascular events and diabetes
- Death from cardiovascular causes
- Quality of Life – as assessed at each follow-up visit by the quality of life instruments EORTC QLQ-C30, QLQ-BLS24 and QLQ-BLM30

An Endpoint Committee of clinicians blinded to treatment allocation will be established to adjudicate on outcomes (except for quality of life).

3.9.2. Statistical Analysis

The statistical analysis aims to address the primary hypothesis. Analysis will be on an intention-to-treat basis. The analysis will consist of two comparisons: firstly all patients randomised to selenium with all those randomised to the associated placebo, stratifying the analysis by the vitamin E allocation; secondly all patients randomised to vitamin E with all those randomised to the associated placebo, stratifying the analysis by the selenium allocation. An interaction is not expected and the data will be investigated descriptively to assess the validity of this assumption.

Kaplan-Meier[167] estimates of recurrence-free and progression-free interval will be used to compare treatment groups descriptively, whilst log-rank tests[168] will be used to test the hypothesis of no difference between treatments. Models for survival data that account for other prognostic factors as well as treatment will also be considered, such as a Cox regression model[102] or a fully parametric one if appropriate. The same methods will be used for the secondary outcome measures.

3.9.3. Sample Size Calculation

Following the recommendation of the Independent Data and Safety Monitoring Committee and the subsequent approval of the Trial Steering Committee, a revised plan which provides justification for a reduced target accrual figure is detailed below.

As a 2x2 factorial design two *a priori* independent hypotheses will be tested, one relating to selenium and one to vitamin E. Using data in a recent meta-analysis on the role of intravesical chemotherapy in Ta/T1 tumours we estimate that the 5-year recurrence rate would be about 45%, or recurrence-free rate of 55%. To detect an absolute increase of 12% in the recurrence-free rate by either of the agents *vs.* their associated placebo (i.e. 55% → 67%) using a log-rank test 460 patients will be needed in total to give 80% power with two-sided significance level of 5%. This calculation is based on an accrual period of 6 years (July 2007 – 2013) and a minimum follow-up period of 3 years. Allowing for an additional 12% for loss to follow-up

would result in a total requirement of 515 patients (compared to 1,200 as was the original figure). The main reasons for this difference include a longer accrual period, a longer mean follow-up period, a change in significance level from 2.5% to 5%, and a change in power from 90% to 80%.

As our recruitment strategy has always been based on the power calculation relating to recurrence rather than progression, we now designate progression as a principal 'secondary' outcome measure: progression will therefore no longer have an impact on sample size calculations.

3.9.4. Frequency of Analysis

An Independent Data Monitoring Committee (IDMC) will review the trial progress after 12 months and interim analyses of the trial data will be presented to the committee for review regularly thereafter. The first published analysis will not occur before all patients in the trial have been followed up for a minimum of 3 years.

3.9.5. Planned Subgroup Analyses

Treatment effects within subgroups defined by tumour stage, tumour grade and smoking status will be investigated. The analysis will be exploratory rather than confirmatory and will include descriptive analysis and a test for heterogeneity of hazard ratios across subgroups.

3.9.6. Trial Stopping Criteria

The SELENIB trial will be stopped if the Trial Steering Committee in conjunction with the Independent Data Monitoring Committee considers that;

- the recruitment rate or data quality are unacceptable, OR
- there are cases of excessive toxicity, OR
- the interim analyses shows differences between treatments that were deemed to be convincing to the clinical community, OR
- significant new information about the trial therapies becomes available, which makes the continuation of the trial (or part of the trial) unethical

SECTION 4: PROJECT B: LONGITUDINAL STUDY OF HEALTH RELATED QUALITY OF LIFE

A longitudinal study of health related quality of life and utility-based patient preference for regular surveillance

4.1. Background

4.1.1. Impact on health related quality of life (HRQL)

As a chronic condition, bladder cancer poses a large burden on patients and health services (see section 1.1). It is therefore surprising that few studies examining the short- and long-term impacts on patients' HRQL have been reported. Botteman et al recently published a review of the literature and identified only three relevant papers. [173] Two of these described the effect of intravesical BCG in 85 Austrian and 30 German patients respectively.[174-175] The main conclusion from these two studies is that despite unpleasant symptoms (mainly urinary) during treatment, severe impacts on HRQL were uncommon. In the third paper, Shover focused on sexual function and cited clinical anecdotal evidence that repeated cystoscopies and intravesical treatment may have adverse psychological effects that led to sexual dysfunction.[176]

We conclude that previous evidence is very limited, especially on the psychological effects of cystoscopic surveillance, and recurrences. This study therefore provides a unique opportunity to investigate these factors longitudinally in a large sample. The results will also be useful for future evaluations of new technologies in surveillance and therapy.

4.1.2. Utility-based patient preference for regular surveillance

Cystoscopic surveillance remains the method of choice to detect recurrences in patients with bladder tumours. Although the negative effect of each individual cystoscopy may not be very large, the overall impact on HRQL may be significant since many patients would have to undergo these tests regularly for the rest of their lives. However, many patients will not have any recurrence after the initial diagnosis. For these patients, accurate prediction using a good prognostic model could spare them unnecessary physical discomfort and psychological stress.

One of the key aims of this programme (specifically Project D) is to develop a prognostic model based on histopathological and molecular markers. We therefore propose to assess patient preference with a utility-based technique, comparing the current regime of surveillance with an alternative follow-up regimen, based on a hypothetical prognostic tool (that is unlikely

to be 100% accurate). Together with data on the effects of repeat cystoscopy, recurrence and progression, the results will be very important if a good prognostic model becomes available which may suggest the possibility of less intensive surveillance in those deemed to be at low risk. In this context we have identified a study that examined patient opinion of urinary tests compared to flexible cystoscopy in bladder TCC follow-up.[177] It found that 89% of patients preferred cystoscopy if the sensitivity of the urinary test was lower than 90%, and 68% of those sampled expected a sensitivity of over 99% before they would opt out of cystoscopic surveillance.[177] However, this very interesting study had its limitations: it was cross-sectional and the sample size was small (n=102, with only 15 women). We therefore propose to examine the preference of patients longitudinally in our cohort.

4.2. Objectives

- To study the effects of recurrence and progression on HRQL
- To study the effects of repeat cystoscopy on HRQL
- To study the patients' assessments of a hypothetical prognostic model and how this affects their preference for the mode of surveillance.

N.B. The second and third objectives are mainly for patients with non-muscle-invasive tumours as most patients with muscle invasive disease will undergo cystectomy.

4.3. Methods

We will use the quality-of-life questionnaires developed by the European Organisation for Research and Treatment for Cancer. The EORTC QLQ-BLS24 with 24 questions specific to non-muscle-invasive bladder cancer and the EORTC QLQ-BLM30 with 30 questions specific to muscle-invasive bladder cancer will be combined and used in conjunction with the general cancer questionnaire QLQ-C30.[178] The bladder specific questionnaires are in the advanced development phase and we will contribute data that can be used for the evaluation of its psychometric properties (Karen West, personal communication).

Assessments using the QLQ-C30 will be made at baseline in the entire cohort of 3,400 patients. Follow-up assessments using the QLQ-C30, QLQ-BLS24 and QLQ-BLM30 [167] will be made at first routine follow-up and annually until the end of study. We have considered the option of limiting the assessment to a sub-sample within the cohort. However, at baseline, one cannot predict which patients will suffer recurrence(s) or progression. We have therefore decided to survey all patients in the cohort to ensure that we have baseline information with annual review on all patients. The HRQL questions feature in section 8 of the baseline questionnaire and section 8 of the follow-up questionnaire (APPENDIX 3).

4.3.1. General description of quality of life over time

The assessments made at various time points during patient follow-up will provide a general description of the quality of life of patients at diagnosis and during the course of the disease. The questionnaires will provide information on physical, emotional, social, cognitive and role functioning as well as a measure of global health status. Measures of general symptoms will also be available, together with measures of the impact of the disease on urinary, sexual, and bowel symptoms.

4.3.2. Assessing the effect of repeat cystoscopy

The EORTC QLQ-BLS24 [167] has specific questions that measure the impact of repeated cystoscopy and intravesical therapy on patients. This will allow an accurate description of changes over time.

4.3.3. Assessing the effect of urostomy and self-catheterisation

Most patients diagnosed with muscle-invasive bladder cancer will undergo a cystectomy and will require a urostomy. The EORTC QLQ-BLM30 [167] has 6 specific questions about the impact of urostomy and one question about self-catheterisation. These questions will allow for measurement of the impact of urostomy and self-catheterisation on patients quality of life over time.

4.3.4. Establishing the effect of recurrence and progression on quality of life

In addition to annual assessments of HRQL, assessments will also be made after recurrence or progression. This will enable the effect of recurrence and progression on HRQL to be established. It will also allow us to ascertain the benefits of selenium and vitamin E on HRQL in “SELENIB”.

4.3.5. Assessing patient preference and utility of hypothetical prognostic models

Our method has been adopted from the Standard Gamble technique.[179] We will question all patients in follow-up sessions with a choice using an additional question (see Section 6 of follow-up questionnaire, APPENDIX 3). The options are to continue repeated invasive cystoscopy or to take a gamble and choose a less invasive prognostic test with two possible outcomes: a true negative prediction with probability p or a false negative prediction with the probability 1-p. The probability of outcomes will be varied until the patient is indifferent about the two alternatives. A measure of the utility of the new prognostic test is the lowest p. This assessment will be taken at the first routine follow-up and then repeated annually. No assessment of this measure will be undertaken at recurrence or progression.

4.4. Data Analysis

The responses from the EORTC questionnaires will be scored according to specified guidelines.[180] The analysis of scores at each time point and in terms of change over time will generally be descriptive. Hypothesis testing will be used for the global health status measure, specifically in terms of changes in score from before and after a recurrence or progression. The utilities of hypothetical prognostic tests will be described. We will investigate whether the perceived utility differs according to sex, duration of disease, recurrence status, and the number of previous cystoscopies.

SECTION 5: PROJECT C: BLADDER CANCER BIOSPECIMEN COLLECTION

To establish a bladder cancer tissue bank to study the predictive effect of molecular and chromosomal factors on the recurrence and progression of bladder TCC

5.1. Background

Establishing a collection of bladder cancer biospecimens

This study will include a large cohort of patients with newly diagnosed bladder cancer. As initial tissue collection will take place prior to definitive histology, tumour tissue, blood and urine will be collected from all patients, regardless of stage. Together with tissues from patients with non-muscle-invasive tumours, we will also collect samples from patients with muscle-invasive tumours and solitary grade 1 pTa tumours. The samples will be stored in a central repository based at the HBRC facility at the University of Birmingham.

Together with detailed linked information on environmental exposures and clinical outcomes, this biospecimen collection will form a unique resource in the UK.

5.2. Objectives

- To establish a bladder cancer biospecimen collection to prospectively store snap frozen and paraffin-embedded bladder tumour tissue for future research into genetic, epigenetic and genomic profiles of bladder cancer. Collected tissue samples will also be utilised in a preliminary study of a panel of molecular markers will be undertaken as part of this protocol (See Project D, Section 6:)
- To prospectively store blood specimens for future research into genomic, epigenomic and serum markers.
- To prospectively store urine specimens for future research into the identification and testing of markers that may be used in screening, diagnosis and surveillance of bladder cancer.

These have been highlighted in a recent review of research priorities by the US NCI. [181] Further details are provided in Appendix 7a.

All future research projects which utilise the BCPP biospecimens will be the subject of separate protocols and ethical submissions, or amendments to the existing protocol.

5.3. Methods

5.3.1. Identifying patients

Informed consent for tissue collection and storage for research and teaching purposes will be sought from all patients recruited into the observational cohort study (Project A1). Details of patient identification and recruitment procedure can be found in section 2.4.6.

5.3.2. Specimen identification and labelling

Specimen tubes/containers will be labelled with a unique specimen number, hospital number, date of birth and study acronym. The specimen number will be used for all bladder tissue, blood and urine specimens collected at the time of the initial diagnosis. The specimen number will include a suffix to identify each individual specimen tube/container. Separate specimen numbers will be allocated for each subsequent recurrence. A Specimen Number Master List matching the patients study number to the specimen number will be maintained by the BCPP Study Office. All processing of samples will be managed via the specimen number in order to ensure that analyses of materials are performed blind. Only designated staff within the BCPP Working Group will be able to access the Master List and thus "back-trace" specimen numbers to patient details. For use in research, either anonymised aliquots carrying only a specimen number will be released, or the hospital number will be redacted from the sample labels at the time of release if the original collection tube is required.

A proforma will be used to document information relating to the collection, processing and storage of all blood, urine and fresh tissue samples collected, providing a full audit trail for each specimen.

5.3.3. Bladder tissue collection and processing

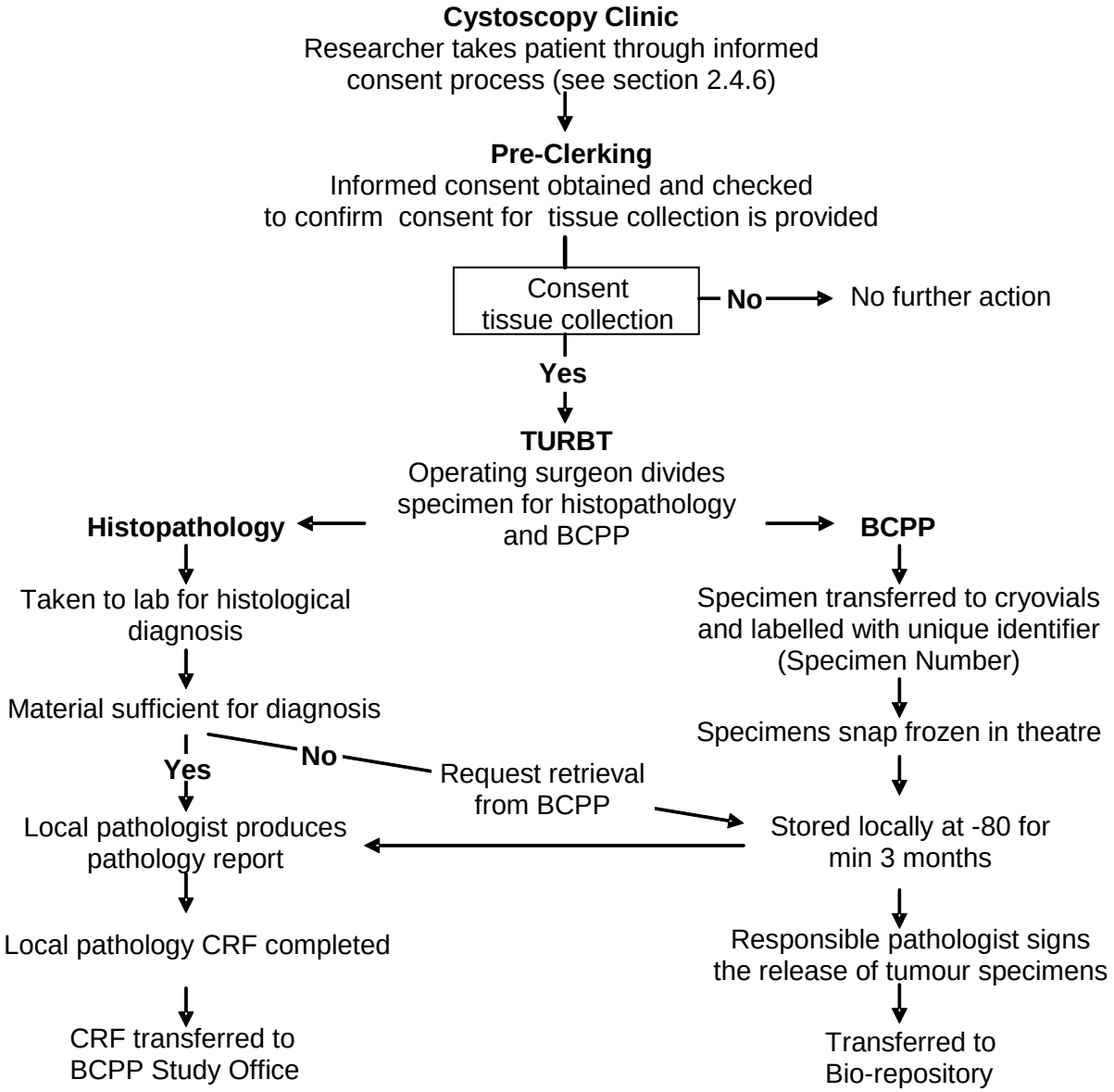
5.3.3.1. Snap frozen bladder tissue

Our researcher will be responsible for tissue collection in the operating theatre. They will have received training on the handling, storage and retrieval of human biological materials including health and safety measures. They will also be required, where applicable, to use appropriate protective clothing and equipment.

Tissue samples for storage will be selected by the operating surgeon, taking into consideration the priority for clinical samples for histopathological diagnosis. They will be separated from the routine pathology samples and placed directly into cryovial storage tubes and snap-frozen in liquid nitrogen for transfer for temporary storage in a dedicated -80°C freezer located within the hospital.

Samples will be periodically transferred from the hospital to the central bio-repository where they will be stored indefinitely in dedicated freezers operating at -80°C. Prior to transfer, the responsible pathologist will be required to sign the release of the specimens. The minimum period that tissue specimens will be kept in the local hospital prior to transfer will be three months. This will enable efficient retrieval and return of specimens should they be required for clinical purposes.

Figure 3: Frozen tissue collection and handling process



5.3.3.2. Paraffin-embedded bladder tissue

Tissue specimens for routine pathological examination are fixed in formalin in the operating theatre and subsequently transferred to the pathology department. The formalin-fixed tissue is processed and one or more paraffin tissue blocks created. These paraffin blocks are then

used to provide tissue sections for diagnostic purposes. For the purposes of the BCPP Project D (SECTION 6:) formalin-fixed paraffin-embedded tissues will be used to generate tissue arrays, which will then be used for immunohistochemistry to stain for a panel of molecular markers. The process of creating tissue arrays involves taking “Tru-Cut” specimens from a paraffin block and following this the paraffin block may be unsuitable for subsequently providing sections for slide mounting. Patients for whom only 1 tissue block exists thus may not be suitable for the collection of tissue for array production. It may nonetheless be possible to take additional unstained slide sections to study expression of individual marker proteins.

To take into account this part of the programme, local pathology departments will be requested to identify a suitable paraffin block (or blocks), provided that there is enough tissue available. This block will be for the use of the programme and subsequently will be stored centrally. Slides from this block will initially be examined under the microscope by the local pathologist to ensure that this tissue is representative of the tumour sample as a whole. If not enough tissue exists in the original specimen to create an extra paraffin block local pathology departments will be requested to create 10 slide-mounted sections for subsequent central transfer and use within the programme.

5.3.3.3. Central Pathology Review Procedures

Following routine local pathological examination and clinico-pathological staging a 10% sample of slides will be transferred for central pathology review. The review will be undertaken by the BCPP pathologists at the Pathology Laboratories of University Hospital Birmingham NHS Foundation Trust. The BCPP pathologists will be blind to the clinical details and local diagnosis. The review diagnosis will provide a stage and grade classifications based on the WHO and WHO/ISUP classification criteria.

The intention of the review is not to alter the clinical diagnosis and management of the patient but to ensure consistency of classification.

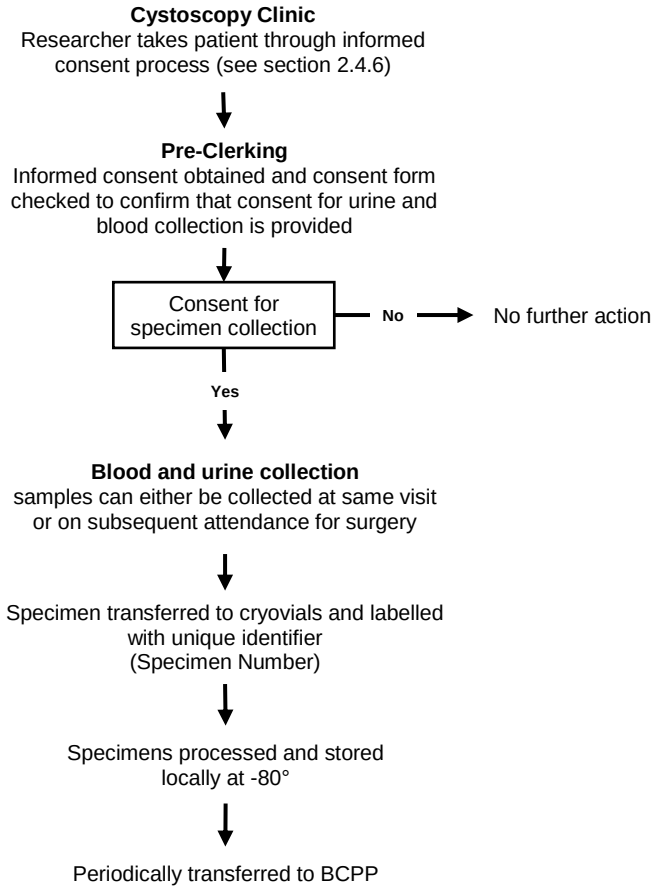
Following central pathology review slides can be returned to the local pathology department if requested. Throughout the pathology review process local units will be able to request the immediate return of the slides if required.

5.3.4. Blood and urine collection and processing

At study entry, blood from all patients will be collected in two 5-ml ETDA tubes and two plain 10-ml tubes. The EDTA treated sample will be stored as whole blood. The sample in the plain tubes will be left to clot, at room temperature for no less than 90 min. After this time the clotted sample will be centrifuged to separate the serum from the red blood cells. The serum

will then be aliquoted labelled and stored at -80°C. Subsequent transfer to the bio-repository will be as for the tissue samples. White blood cells will be separated by standard methodology (e.g. “Lymphoprep”) and frozen and stored at -80°C for subsequent DNA extraction either locally, or at the HBRC, or by third parties providing this as a service (giving a non-tumour/germline DNA control for each patient). There will be no further collection of white blood cells after baseline other than to replace missing or technically inadequate samples.

Figure 4: Blood and urine collection and handling process



Urine samples will be collected for each patient during routine pre-clerking. The urine will be collected using a centrifuge tube. The urine will be centrifuged to separate residues such as cellular debris or urate crystals. The supernatant will be aliquoted into pre-labelled cryovials and frozen at -80°C. The urine residue may also be stored. Urine samples will be transferred to the bio-repository as for blood and tissue samples. Urine volumes and concentrations will be normalised by measurement of urine protein and creatinine concentration. Urine pH will also be measured at the time of collection. Evidence of a urinary tract infection will be documented on the CRF to be included in subsequent analysis.

5.3.5. Transfer of specimens to the BCPP biospecimen collection

All specimens will be stored locally until such a time that the responsible pathologist is satisfied that clinico-pathological requirements have been fulfilled and that the specimens can be dispatched for central storage. It is anticipated that this will be a minimum period of 3 months post surgery. Periodically the responsible pathologist will be asked to give signed authorisation for the release of a batch of specimens. A detailed log of all transferred specimens will be provided to the authorising pathologist. The transfer of specimens from local sites to the central biorepository will be coordinated by the research nurse at the individual urology unit.

The specimens for transfer to the BCPP biorepository will comprise:

- Paraffin tissue block (for creating tissue arrays)
- Snap-frozen bladder tumour samples
- Blood samples
- Urine samples

In order to integrate the central pathological review process, haematoxylin and eosin slides may be requested for transfer at the same time as specimens required for the biorepository.

5.3.6. Retrieval of specimens from the BCPP biorepository

The location of specimens will be tracked by a computerised system. Should any specimen be required to be returned to the local site for further clinico-pathological staging or due to patient withdrawal of consent, the relevant sample will be speedily retrieved from the biorepository and returned to the local pathologist.

5.3.7. Specimen collection standard operating procedures

The process of collection, handling, routing and storage of specimens will be controlled by one common set of standard operating procedures (SOP's). The SOP's will ensure full compliance with relevant legislation including the Human Tissue Act, the European Union Trials Directive and associated codes of conduct for Good Clinical Practice (GCP) and Good Laboratory Practice (GLP).

5.3.8. Biospecimen collection quality assurance

Ensuring the quality of the specimens collected will be an essential part of the BCPP. Biospecimen quality assurance will be a continuous process throughout the life of the programme to ensure that none of the collected specimens will be wasted. It is anticipated that the evaluation of specimen quality will take place on an annual basis, and will involve the

evaluation of at least 10% of all the tissues collected during the life of the programme. Furthermore, specimens may be used frequently for translational research (Appendix 7a), and these studies will also provide evaluations of specimen quality.

SECTION 6: PROJECT D: STUDY OF THE PREDICTIVE EFFECT OF A PANEL OF MOLECULAR MARKERS ON RECURRENCE OR PROGRESSION OF BLADDER CANCER

6.1. Background

6.1.1. The need for a good prognostic model based on molecular markers

In current practice, the majority of patients with non-muscle-invasive tumours are subject to frequent follow up by cystoscopy, many for the rest of their lives. A prognostic tool that can accurately identify those who are very unlikely to suffer recurrence or progression could spare patients unnecessary invasive procedures and psychological burdens. There could also be enormous cost savings for health services.

Currently, histopathological factors only provide very crude prognostication. In this regard, molecular markers could represent a potential basis for refinement. Such markers may also help to identify patients at high risk of relapse who may benefit from adjuvant therapy. Furthermore, these molecules may provide the targets for novel therapies.

6.1.2. Limitations of the research to date on the use of molecular markers for prognostication

Research in this area has not yet resulted in assisting therapeutic decisions or prognostication. [182] We believe there are at least two main reasons behind this:

<u>Methodological</u>

One important principle of research requires that hypotheses be stated in advance. Unfortunately, it is rare to find clearly stated hypotheses in prognostic factor studies in bladder cancer. As a result, in the literature there are numerous reports on the effect of single markers on which no *a priori* hypotheses were stated when the tissues were collected. Such studies can only be regarded as exploratory and any positive results would need to be confirmed. Previous work is also limited methodologically by small sample sizes, inadequate validation, inadequate clinical follow up, use of different cut-off values, and failure to adjust for known predicting factors.[182-184] This sad state of affairs led Schmitz-Drager et al to provocatively label the field as the “playground of urology scientists”, using p53 immunohistochemistry as a specific example. [185]

<u>The complexity of tumour development</u>

Carcinogenesis involves multiple genetic, epigenetic and cellular changes and so reliance on single markers would almost certainly fail to result in large predictive power.[182;186]

Identifying suitable molecular markers

Our group recently conducted a systematic review of molecular markers in bladder cancer. We have identified those markers for which there has been the strongest or most consistent evidence suggesting that they may be useful in predicting recurrence and progression.[12] Some well-studied markers have been omitted from our list as we felt that the evidence for their role was inconclusive. A detailed description of our panel of 7 markers can be found in APPENDIX 7. A summary of these markers is presented in table 1.

Table 4: *Over*view of molecular markers associated with bladder cancer recurrence or progression

Markers	Hypothesised predominant effect(s)	Number of patients in largest study to date	Reference for method to be used
FGFR3	Recurrence and progression	112	119
EGFR	Progression	101	156
pRB	Progression	363	157
p53	Recurrence and progression	164	157
Ki-67	Recurrence and progression	319	157
VEGF	Recurrence and progression	185	158
CK20	Recurrence	58	159

6.2. Objectives

- To evaluate the prognostic role of a panel of markers chosen *a priori* in a large prospective study using prospectively collected tissues, which will be analysed by standardised and validated methods

6.3. Methods

6.3.1. Immunohistochemistry (IHC)

IHC on tissue arrays will be used to detect the expression of these markers (except FGFR3). The rationale for this technique is twofold: IHC is a technique that is used in NHS histopathology laboratories nationwide and is thus highly clinically applicable; tissue arrays facilitate the handling of large numbers of tumour samples, thus enabling large-scale screening of these molecular markers.

6.3.2. Tissue Arrays

This new technique allows a large number of samples from different patients to be presented on the same slide, thus enabling the large scale screening of samples by IHC. Representative areas of tumour material from paraffin wax blocks (up to a maximum of four per tumour) are

selected for subsequent incorporation into tissue arrays. These are constructed by acquiring cylindrical ("Tru-Cut") biopsies from individual paraffin-embedded tumour tissues into a tissue array block. A subsequent single immunostaining reaction provides information on all of the specimens on the slide. We plan to use a modified method of array preparation to include fewer (50) but larger (5mm diameter) samples per array to reduce the possibility of bias from small sample size.

Patient samples will be identified from pathology records and the archive haematoxylin and eosin (H&E) slide examined for a suitable region of interest. A "Tru-Cut" core corresponding to a representative region will be taken from the tissue blocks and mounted in normal liver, which is used as the support medium on the tissue array slide. 5mm "Tru-Cut" needle cores will be taken from each tumour block to construct tissue arrays, each comprising 50 different tumours. The array block is subsequently sectioned and stained. Staining will then be assessed and reported by two pathologists, assessing the sections independently. To allow for tumour heterogeneity, antibody optimisation and experimental errors, a total of four cores from each block will be taken to create four different sets of tissue arrays from this group of patients. This technique greatly reduces the work involved in screening large numbers of samples and facilitates inter-comparison between different samples by eliminating variations due to staining techniques.

6.3.3. PCR-SSCA

For FGFR3 mutations, DNA will be extracted from paraffin-embedded tissue followed by PCR-SSCA (single-strand conformation analysis) to screen for mutations in exons 7, 10, 15, and 19 of the FGFR3 gene. [187]

It is feasible, however, that the approaches outlined above may be superseded during the life of BCPP and our approach to the identification of prognostic and predictive markers may need to be amended.

6.4. Statistical considerations

6.4.1. Data Analysis

The statistical investigation of specific prognostic markers and the development of a prognostic model will take full account of current thinking regarding the development of reliable prognostic models.[188-189] We will model continuous markers using fractional polynomials. We will explore both parametric and non-parametric models. The independent and joint effects of markers will be examined in a multivariate manner, adjusting also for environmental exposures and known (mainly histopathological) prognostic factors. In patients

participating in the SELENIB trial (Project A2), selenium and α-tocopherol status would also be taken into account in data analysis. This will be performed by independent statisticians so as not to break the blinding.

We will make use of resampling methods (bootstrapping) to investigate the stability of the derived model.[190] We would use the data set to attempt to validate pre-existing models for prognosis in bladder cancer derived from an individual patient data meta-analysis of randomised trials.[191-192] Although high quality, these data would not be useful for reverse validation because of absence of information on all the relevant variables.

6.4.2. Sample size

With 3-year recruitment, median follow up of 36 months (range 18-54 months) and 5% loss to follow up, a sample size of 1,600 non-muscle invasive bladder cancer patients would give us 80% power (2-sided α = 0.01, allowing for multiple comparisons) to detect the following effects associated with the markers:

Table 5: Molecular markers - effect size estimates

Prevalence of markers (%)	**Rate ratio detectable**	
	Recurrence*	Progression[#]
10	≥ 1.77	≥ 2.12
50	≥ 1.47	≥ 1.68
90	≥ 1.92	≥ 2.39

*assuming 25% in reference group
[#] assuming 13% in reference group

We will therefore have very good power to detect associations that are likely to be of significant clinical utility. Our sample size is also more than four times larger than the largest individual studies on single markers to date. This implies that almost all previous studies have been underpowered, with substantial risks of false positive findings given the multiple comparisons made in the absence of *a priori* hypotheses.

SECTION 7: PRACTICAL ORGANISATION OF THE PROGRAMME

7.1. Sponsorship

The University of Birmingham undertakes the role of Sponsor for the Bladder Cancer Prognosis Programme and SELENIB trial. The sponsor delegates all aspects of management and co-ordination of the study to the BCPP Working Group.

7.2. The BCPP Working Group

This study is funded by Cancer Research UK and conducted by The Department of Public Health and Epidemiology and the CRUK Institute for Cancer Studies, University of Birmingham (CRCTU). The BCPP Working Group forms the Cancer Research UK Bladder Cancer Group.

The programme will be centrally co-ordinated and managed by the BCPP Working Group, which is a multidisciplinary collaborative group comprising clinical and academic members of University of Birmingham and University Hospitals Birmingham NHS Trust. The group, led by the Chief Investigator, comprises urologists, oncologists, pathologists, molecular biologists, epidemiologists and statisticians (a full list of BCPP Working Group members can be found on page 2).

The team is based within the BCPP Study Office within the Institute of Cancer & Genomic Sciences at the University of Birmingham. Most of the laboratory and statistical work will also be carried out in the Insitute of Cancer & Genomic Sciences, although a number of collaborations with other universities and organisations within the European Economic Area may also be undertaken (see Appendix 7b for a list of external collaborators). Frozen BCPP biospecimens will be hosted by the Human Biomaterials Resource Centre (HBRC) at the University of Birmingham, a Human Tissue Authority licensed facility. Formalin-fixed paraffin-embedded blocks and sections will be maintained in secure storage areas of the Insitute of Cancer & Genomic Sciencesat the University of Birmingham.

The BCPP Working Group will be responsible for the application for ethical approval, setting up participating centres and continued liaison with and support for the centres. The team will be responsible co-ordinating data and tissue sample collection; tissue, blood and urine banking; data analysis; publication and reporting to ethical and regulatory authorities. The programme will be managed day-to-day by the BCPP Study Co-ordinator under the leadership of the Chief Investigator. The Study Co-ordinator is responsible for the management and

supervision of the research team members in collaboration with clinical managers located within the centres.

The Study Co-ordinator will establish and oversee the data capture process and will also monitor the data integrity and completeness. The Study Co-ordinator will provide regular reports on performance and data quality to the BCPP Working Group.

7.3. SELENIB Trial Steering Committee

A Trial Steering Committee (TSC) will be established to monitor and supervise the progress of the trial. The role of the TSC is to provide overall supervision of the trial on behalf of the funding body. In particular, the TSC will concentrate on the progress of the trial, adherence to the protocol, patient safety and the consideration of new information. Day-to-day management of the trial is the responsibility of the BCPP Working Group.

Membership of the TSC will include an independent Chairman, two other independent members, the Chief Investigator and one or two other members of the BCPP Working Group. The TSC will aim to meet annually. The Trial Co-ordinator and Statistician will attend meetings as appropriate. Observers from the funding body and, if applicable, Host Institutions or sponsors will be invited to TSC meetings.

The independent members of the TSC for the SELENIB trial are:

Chairman

Professor N. Clarke
Consultant Urologist
Department of Urology
Christie Hospital
Wilmslow Road
Manchester M20 4BX
Email: noel.clarke@srht.nhs.uk

Independent Members

Professor B. Kiemeney
Professor of Epidemiology
Department of Epidemiology and Biostatistics
University Medical Center Nijmegen,
P.O. Box 9101 (HP 133 EPIB)
6500 HB Nijmegen
Email: B.Kiemeney@ebh.umcn.nl

Professor P.U. Malmström
Specialist Urologist
Department of Urology
University Hospital
Uppsala
Sweden
Email: Per-Uno.Malmstrom@surgsci.uu.se

7.4. SELENIB Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be set up to monitor the progress of the trial. They will meet at regular intervals as they see fit. Members of the IDMC will include an independent Statistician, Urologist and Oncologist.

The role of the IDMC will be to ensure that unanticipated differences in treatment can be detected early, any unexpected toxicity can be addressed promptly, and the trial is modified or stopped when necessary (see section 3.9.6).

The Trial Statistician will provide the IDMC (but not the BCPP Working Group) with a report summarising the un-blinded data. The Working Group will be provided with an update on recruitment and patient characteristics only and will attend for whatever part of the meeting the IDMC wishes. Information on the main endpoints of the trial will be kept strictly confidential.

The report will be submitted to the IDMC at least annually and upon reaching the accrual target, however, the IDMC will advise on the frequency of reviews of the data on the basis of accrual and event rates.

Following a review, a confidential report will be made in writing by the IDMC to the Trial Statistician. A separate report will be sent to the BCPP Working Group which should not convey the interim results of the trial. It will be the responsibility of the Working Group to decide whether or not to act upon the information received from the DMC.

The IDMC will be notified of all amendments to the trial protocol or any problems, including organisational issues, with the trial. The IDMC will also consider any major new information from other sources considered relevant to the trial.

7.5. Centre Participation

To participate in the research programme each institution should nominate one responsible urologist who will undertake the role of Principal Investigator for the study at their institution. Centres wishing to participate in the BCPP study should first complete and return to the BCPP Study Office a BCPP Site Participation Form (See **Error! Reference source not found.**). In

addition, prior to randomising the first patient onto the SELENIB trial, the centre must also complete and return a Study Site Agreement Form (0). The BCPP Working Group will undertake a process of site appraisal, investigator consultation and site set-up prior to the launch of the programme at each institution.

7.6. Ethical Considerations

The Chief Investigator will be responsible for ensuring that multi-centre ethical approval is obtained.

The Principal Investigator at each centre will be responsible for ensuring that this study is conducted in agreement with the Declaration of Helsinki (0) and that local ethical committee and R&D Directorate approval are obtained. The Study will be conducted in accordance with the principals of the ICH Guidelines on Good Clinical Practice.

Patients will be required to give written informed consent prior to entry into BCPP/SELENIB (consent process detailed in section 2.4.6). Information sheets (APPENDIX 1), prepared in accordance with COREC guidelines, it is anticipated that study information will be given to patients at least 24 hours before written consent is requested.

7.7. Patient withdrawal

Patients participating in BCPP and the SELENIB Trial will be advised of their right to withdraw from the study as part of the informed consent process.

Upon withdrawal, patients will not be required to attend any further study-specific follow-up appointments or complete any further questionnaires. Patients will be asked whether they wish for the data and biological specimens collected up to the point of withdrawal to be retained and used for their intended purpose. They will also be informed that further follow-up data may be collected after their withdrawal from medical notes, NHSCR central register and the Office for National Statistics.

All specimens and data relating to the patient will be retained unless the patient specifically requests their destruction. In such instances, study numbers will not be reallocated. Stored tissue samples which have not yet been used for their intended purpose will be returned to the local pathologist. Blood and urine samples which have not yet been used for their intended

purpose will be destroyed. Destroyed specimens will be replaced by a tracer for audit purposes. Specimen numbers will not be reallocated.

Patients participating in the SELENIB Trial will be asked to return unused treatment packs to the research nurse who will then return the packs to pharmacy for destruction.

7.8. SELENIB - Clinical Trial Authorisation (CTA)

The Chief Investigator is responsible for ensuring that the Investigational Medicinal Products (IMP's) used in the SELENIB trial are covered by a Clinical Trial Authorisation.

7.9. Practical Administration

7.9.1. The Protocol

One common protocol will be used at all participating centres. The finalised master protocol will be held at the BCPP Study office. Any amendment to the protocol will be co-ordinated by the BCPP Working Group. Amendments will be submitted to the appropriate regulatory and ethical authorities for approval. Upon approval, amendments will be circulated to all centres incorporated in a fully re-printed copy of the protocol. A full audit trail of such amendments will be maintained. A process of document control will be implemented to provide assurance that all copies of the protocol that are in circulation are current version. A shortened summary protocol will also be created for use in clinical areas, containing the parts of this protocol most pertinent to the clinical management of patients.

7.9.2. Questionnaires

One common set of questionnaires will be used at all participating centres (see APPENDIX 3). The questionnaires have been piloted initially within the BCPP Working Group and lay-members of the public. Following ethical approval, the questionnaire will be further tested amongst bladder cancer patients recruited into the study at the first recruiting centre prior to the programme being rolled out to other sites. As a measure of quality assurance, the patient will be asked to verify that the data is correct by signing and dating each questionnaire.

7.9.3. Case Report Forms (CRF's)

One common set of forms will be used at all participating centres. CRF's will be used to capture clinical data directly from source documents (see 0). Source data verification will be undertaken on a random sample of patients. All data will be subject to systematic data

checking. Any queries detected by the BCPP Study Office will be fed back to the centres for resolution.

7.9.4. Data Collection

The database for the study will be held at the BCPP Study Office located within the University of Birmingham. Paper copies of all questionnaires, CRF's and supplementary clinical documentation will be stored both locally in the centre and in the BCPP Study Office.

7.9.5. Confidentiality of patient data

All data collected as part of the BCPP will be handled according to the Data Protection Act. The use of names as patient identifiers on paper forms and the study database will be limited. Where possible, an abbreviated patient identifier will be used in place of the patient name. Within the BCPP Study Office and at each participating site, patient identifiable documentation will be held in locked cabinets. The cabinet itself will be accessible only to authorised personnel. Any electronic correspondence containing patient data will be password protected and encrypted. All study personnel will be required to sign a confidentiality undertaking.

No personally identifiable information will be released from the BCPP Study Office. Limited clinical information may be passed on to researchers within the European Economic Area. It would not be possible to identify any patient from this information and any information provided will be handled according to the normal standard of medical confidentiality and data protection.

7.9.6. Data collection and security procedures

Where possible, data will be captured and transferred between the local hospitals and the BCPP Study Office via BCPP laptops operating on a virtual private network (VPN). The VPN will enable the laptops to log directly onto the dedicated BCPP server, located at the University of Birmingham. The VPN will be accessible only to authorised BCPP personnel when the username and password is entered. The VPN will transmit snapshot keystroke data via HTTPS secure web-pages using 128 mega-bit encryption. The use of a VPN ensures that no patient data will be stored on laptop hard-drives. The security afforded by this system is on a par with that of UK online banking systems.

Data stored on the dedicated BCPP area of a server within the University of Birmingham will be protected by firewalls at both university and server room level. Load-balancing between two sites will be implemented to ensure that the VPN will function in the multi-user environment and will provide complete redundancy. The server rooms will only be accessible by authorised key holders within the IT team. The building in which the servers are located will

additionally be restricted to authorised university personnel. Back-up tapes will be taken daily and will be stored in an onsite fireproof safe located within the server building.

The electronic transfer of encrypted data would, in all cases, be backed-up by a paper hard-copy. One copy will be sent to the BCPP Study Office and another copy will be stored locally in the site-file. The site file will be kept within a locked filing cabinet accessible only to authorised BCPP personnel.

Where electronic data transfer is not possible, a paper-based system will be implemented. The paper-based system requires completed paper copies of questionnaires and CRF's to be sent to the BCPP Study Office for data entry.

Transportation of all printed documents containing patient identifiable data will be undertaken according to local trust policy on postage of confidential data.

7.9.7. Use of translation / interpreters

Depending on local guidelines, patients who do not have a good understanding of English will not be excluded from the study. However, we do not plan to provide written translations of questionnaires as no validation testing has been undertaken to ensure that translation does not affect the semantics of the questions. Also, when completing the questionnaires, the patient must be able to communicate verbally with the researcher to ask for clarification and to respond to questions. Where completion of the questionnaires can be achieved with the help of interpreters this will be encouraged.

If interpreters are used, it is important that they are available at each consultation and study visit as accurate and adequate information is required from the patient as part of the study procedures. If family members are used and/or NHS interpreters, this requirement will be discussed and it would be the local investigator's responsibility to arrange these services prior to patient entry into the study.

Patients unable to participate in the observational research (Project A1 and B) would still be considered eligible for the associated molecular pathology studies as well as the linked SELENIB trial.

7.9.8. Monitoring and quality assurance

Trial conduct will be monitored by site visits by the Study Co-ordinator (and/or other members of the BCPP Working Group) or by monitors appointed by the University of Birmingham and as described in a Monitor Plan. These site visits will include a random selection of patient

informed consent forms, and source data verification of a random sample of patients' files. This process will involve comparing data contained in the CRF with source data from the medical notes. Numbers of patients monitored will be determined in the Monitor Plan.

Data submitted via CRF's will be subject to systematic validation at the point of data entry. Manual checking will also be undertaken centrally within the BCPP Study Office. In addition, there will be periodic clinician reviews of CRF data.

7.9.9. Monitoring Arrangements for SELENIB Trial

Monitoring of eligibility, consent, SAE reporting, drug accountability, protocol compliance and data quality will be performed according to the Monitor Plan. All monitoring activity will be documented in the Monitor Plan and Monitoring Visit Reports.

7.9.10. Access to BCPP data

BCPP data may be made available to individuals subject to ethical approval and permission from the BCPP Working Group. Requests to the BCPP Study Office should include the following information:

- Reason for data request, specifying question(s) to be answered
- Documentary evidence of ethical approval of the research project
- Required data (item and in which form)
- Proposed method to be used when working with the data (define file specification)
- Whether there are any objections to involvement of the BCPP statistician. If so outline the reason for the objections.
- Which other committees are informed/involved
- If the data are going to be published, an agreement to name those people relevant to the study
- An agreement to adhere to the BCPP publication policy and to notify the BCPP Working Group of any resulting publications

7.9.11. Access to Specimens within the BCPP Tissue Bank

Access to specimens stored within the BCPP Tissue Bank may be made available to individuals subject to ethical approval and permission from the BCPP Working Group. Requests to the BCPP Study Office should include the following information:

- Reason for specimen request, specifying question(s) to be answered
- Documentary evidence of ethical approval of the research project
- A clear description of which specimens are needed

- Proposed method to be used when working with the specimens (define laboratory technique and tests to be performed)
- Whether additional clinical data are required (if so, please also refer to section 7.9.10)
- Which other committees/organisations are involved
- If the resulting data are going to be published, an agreement to name those people relevant to the study
- An agreement to adhere to the BCPP publication policy and to notify the BCPP Working Group of any resulting publications

7.9.12. Publication Policy

Publication using data from the BCPP must be agreed between the main author of the manuscript or abstract and the full BCPP Working Group before starting the work, so that authorship can be discussed within this group prior to preparation of any publications. All manuscripts and abstracts and other documents that contain data arising from the BCPP must be submitted to the BCPP Working Group for approval prior to the deadline for conference submission. All abstracts and papers must have written approval from the study management committee prior to final submission.

All persons designated as authors should qualify for authorship. Every author should have participated sufficiently in the work to take public responsibility for the content. At an appropriate place in the article one or more statements should specify contributions that need acknowledging for general support, technical help, financial and material support etc.

7.9.13. NCRI Bladder Cancer Studies Group

The NCRI Bladder Cancer Studies Group will be kept informed of progress with the project and the linked SELENIB trial (Project A2). Both this project and the SELENIB trial have NCRI approval by virtue of the peer-reviewed funding from CR UK.

7.9.14. End of Trial

For the purposes of Clinical Trial Authorisation (CTA) under the European Union Directive 2001/20/EC, the study is deemed to have ended when patient follow-up ends i.e. at the date of last data capture. This is anticipated to be 31st December 2016.

For the purposes of Research Ethics Committee approval, the study end date is deemed to be the date of last data capture.

APPENDIX 1
PATIENT INFORMATION SHEETS AND CONSENT FORMS

1. BCPP Patient Consent Form (Version Number 2.0, August 2009)
2. BCPP Patient Information Sheet (Version Number 2.0, August 2009)
3. BCPP Patient Information Flip Chart (Version Number 2.0, August 2009)
4. BCPP General Practitioner Information Sheet (Version Number 2.0, August 2009)
5. SELENIB Patient Information Sheet – Short Version (Version Number: 2.0, August 2009)
6. SELENIB Patient Information Sheet – Full Version (Version Number: 2.0, August 2009
7. SELENIB Patient Information flip chart (Version Number 2.0, August 2009)
8. SELENIB Consent Form (Version Number 2.0, August 2009)
9. SELENIB General Practitioner Information Sheet (Version 2.0, August 2009)

TO BE PRINTED ON INSTITUTION HEADED PAPER

Bladder Cancer Prognosis Programme (BCPP)

Cancer Research UK Bladder Cancer Research Group

Chief Investigator:	**Dr Rik Bryan** **University of Birmingham**
Name of your Doctor:	**<Name of urologist>** **<Hospital name>**

PATIENT INFORMATION SHEET

(Version Number: 2.0, August 2009)

We would like to invite you to take part in a clinical research study.

We are currently recruiting patients who have a bladder abnormality that is suspicious of bladder cancer.

Taking part in this study is entirely voluntary. Before you decide whether you would like to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this information leaflet.

1. What is the purpose of the study?

For the majority of patients who are diagnosed with bladder cancer, regular check-ups are required for the rest of their lives, so that if the cancer returns it can be detected early. These check-ups involve an examination of the bladder using a thin tube with a light inside that is inserted into the bladder through the water pipe (urethra). This procedure is called cystoscopy.

The dilemma for Urologists treating bladder cancer is that some bladder cancers need very frequent cystoscopies and others can be considered to be less harmful. Unfortunately, our current tests do not yet allow us to accurately predict at the outset how a patient's bladder cancer will behave in the future.

Here in the West Midlands we are undertaking a programme of research (funded by Cancer Research UK) to investigate if we can improve our ability to predict how a patient's bladder cancer will behave. This research will involve studies on your blood, urine, bladder tissue and nail clippings (these allow us to measure levels of various natural minerals contained within the body). We will use these samples to study some genetic and biological factors. We will also collect some personal details and lifestyle information using questionnaires. This information will help us to look into factors that can influence the way in which bladder cancers behave.

In order to find out if any of these factors are important, we will need to monitor your progress over the next 5 years and collect information from you regularly during your routine follow-up visits to hospital.

2. Why have I been chosen?

You have been diagnosed with a bladder abnormality that is suspicious of bladder cancer. We are hoping to collect information on patients who have been newly-diagnosed with a bladder abnormality that is suspicious of bladder cancer and who meet the requirements of the study. We intend to study at least 3400 patients over the next 3-5 years.

3. Do I have to take part?

It is up to you to decide whether or not to take part. You do not have to decide straight away. You can take this information sheet away with you. When you return to hospital before your operation, you will be asked if you would like to participate in the study. If you agree to take part you will be asked to sign a consent form. If you do decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive or your relationship with your doctor.

4. What will happen to me if I take part?

Once you have agreed to take part and have signed a consent form, the study will run alongside your standard bladder cancer treatment. When you come into hospital before your bladder operation, our researcher will talk to you about the study and will take you through a questionnaire. The questions will be on your background, medical history and lifestyle. We would need you to give us about an hour of your time to fill in this questionnaire. Before your operation we will take samples of your blood and urine.

During your operation pieces of tissue from your growth are removed from the lining of the bladder. This tissue will be sent to the pathologist at your hospital for detailed analysis under a microscope as part of your standard care. For the purposes of this study we will use a small sample of the tissue that is removed.

If the microscope analysis confirms that you have bladder cancer and if the cancer is suitable, we would then like to collect information from your medical records on any further bladder cancer treatment that you receive. After your operation we will send you a questionnaire which asks about your family history of cancer, your previous occupations and the places where you have lived. This questionnaire should take you about half an hour to fill in. We will also send you a food diary so that you can keep a record of what you eat and drink in a one week period.

We will monitor your progress at your regular hospital follow-up visits. This monitoring would involve completing a short questionnaire at the time of each follow-up visit. This follow-up questionnaire will require approximately half an hour of your time to fill it in. If it is not possible to fill it all in when you attend your follow-up appointment, we may need to telephone you at home to collect the rest of the information. If your bladder cancer returns we would once again like to take samples of your blood and urine and bladder cancer tissue. We would like to monitor you in this way for a total of 5 years.

Following your operation and depending on the outcome of the pathologist's diagnosis, we may also wish to ask you to take part in a randomised trial (our researcher will discuss this with you, if appropriate). If, after your operation, you are <u>not</u> diagnosed as having a bladder cancer, we will not ask you to participate further in this research project.

5. What do I have to do?

Other than your normal treatment, we would need you to complete our questionnaires and let us have samples of your blood, urine and nail clippings. You would also be asked to give

permission for us to use some samples of the abnormal bladder tissue that is removed during your operation.

6. What will happen to the tissue and blood samples taken as part of this study?

The bladder tissue, blood and urine that will be collected as part of this research study will initially be stored locally at your hospital and then transferred to a central bio repository for long-term storage. Nail clipping collected will be stored centrally at the University of Birmingham.

We aim to collect together, from all of the patients who enter this research study, a large 'bank' of bladder tumour samples. The samples collected will be used, first and foremost, for research as part of the BCPP study. Such a collection or 'bank' of samples may also be very useful for research in the future that will help us to understand more about how bladder cancers behave. We would like to store and later use the samples donated as part of this study for future research, although such research projects have not yet been planned and could occur many years in the future. These future research projects may involve studies of your genes and DNA. By giving your consent for your bladder tissue, blood, urine and nail samples to be stored in the 'bank' you will be offering your samples as a gift. If, after your operation you are diagnosed as not having bladder cancer, we would still like to keep your samples for further use in approved research.

The sample stored for research will be taken from samples that remain after all the information needed by doctors diagnosing and caring for you have been obtained. The tumour, blood and urine samples are stored under strict security and are given a code, so that researchers receiving the samples do not know your name or any other personal details. Researchers who wish to use the samples that are stored in the bank will only be given access to the samples after their research has been approved by an independent Research Ethics Committee who make sure that the research is in the interest of patients and is carried out safely.

7. What are the possible disadvantages and risks of taking part?

There are no foreseeable risks of taking part. This study will run alongside your routine bladder cancer treatment and follow-up; it will not influence this process.

8. What are the possible benefits of taking part?

There is no intended immediate clinical benefit from taking part in this study. However, the information obtained from this study may result in changes in the future diagnosis, treatment, and follow-up of patients with bladder cancer. These changes may also benefit you.

9. What if new information becomes available?

This study does not influence your routine bladder cancer treatment and follow-up. However, any new discoveries or information relating to this will automatically be incorporated into the standard treatment provided by your doctors.

10. What happens when the research study stops?

When the study stops your routine bladder cancer treatment and follow-up will continue in the normal way, although it may incorporate new discoveries or information generated by this study.

11. What if something goes wrong?

As this study does not influence your routine bladder cancer treatment and follow-up, the normal National Health Service complaints mechanisms should be followed.

12. Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. If you agree to take part in this study we will need you to sign a consent form. You will be given a copy of the consent form and this information sheet to keep.

With your consent, we will be informing your GP about your participation in this study. Authorised professionals, other than those involved directly in your care, may inspect your medical notes. Information contained within your medical notes would be used only for the purposes of collecting information about your treatment and to check that the research is being carried out correctly. These authorised professionals include members of the BCPP (Bladder Cancer Prognosis Programme) research team and regulatory authority representatives.

We would like to collect some contact details from you including your current address, and telephone number. We would like to collect these details so that we can send a questionnaire to you at home and so that we can contact you before an appointment to remind you if you need to bring anything in with you to the hospital. Your contact details will be kept strictly confidential and only members of the BCPP research team would be allowed access to them.

Information on all patients entered into this study will be sent to the BCPP Study Office which is located at The University of Birmingham where it will be retained in secure storage and handled according to the 1998 Data Protection Act. No personally identifiable information will be released from the BCPP study office. Limited clinical information may be passed on to researchers within the UK. It would not be possible to identify any patient from this information and any information provided will be handled according to the normal standard of medical confidentiality and data protection.

13. What will happen to the results of the research study?

Important results from the study will be published as they become available, which may be during the course of the study or after the study has finished, and this could possibly take several years. We intend that any results will be published in peer-reviewed journals or will be presented at meetings involved with this field of cancer research, and these publications will be available upon request from your specialist doctor. You will not be identified in any report or publication.

14. Who is organising and funding the research?

The research is being organised by The Department of Public Health and Epidemiology at The University of Birmingham, in collaboration with the Cancer Research UK Institute for Cancer Studies at The University of Birmingham, The Department of Urology at The Queen Elizabeth Hospital, Birmingham, and participating Urology Departments within the West Midlands. The research is funded by Cancer Research UK. The doctors conducting this study are not being paid for including and looking after you within this study.

15. Who has reviewed the study?

This study has been reviewed by the Nottingham Multi-centre Research Ethics Committee and by scientific experts at Cancer Research UK.

16. What if I have other concerns or would like further information?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the Urologist or the BCPP researcher at your hospital -details listed

below. If you would like advice from someone independent of the study concerning your participation, you should contact <e.g. Urology CNS>.

Finally, thank you for taking the time to read this information sheet and for taking part in the study, if you agree to do so.

Contact Details:

BCPP research team member: <Research Nurse/Trial Practitioner> **Tel.:** <contact number>

Local Investigator: <Urologist> **Tel.:** <secretary's contact number>

NOTE: This flipchart is to be used as a discussion guide during the informed consent process, in addition to the printed Patient Information Sheet, to ensure that study information is clearly and accurately presented both verbally and in writing.

Bladder Cancer Prognosis Programme
"BCPP"

Patient Information Flip-Chart

UNIVERSITY OF BIRMINGHAM

CANCER RESEARCH UK

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

BCPP Introduction

- **The Bladder Cancer Prognosis Programme or "BCPP" is a clinical research study across the West Midlands involving approximately 3500 patients thought to have bladder cancer**
- **We are particularly interested in what we can do to prevent bladder cancers from coming back (recurrence) after they have been treated**
- **And to investigate if we can improve our ability to predict how bladder cancer will behave in the future**

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

BCPP Summary

- **In order to provide better health care for bladder cancer patients we would like to ask you for some information about…..**
  - **your lifestyle**
  - **your health and**
  - **your feelings**
- **We would also like to ask your permission for a sample of your bladder tissue, blood, urine and toenail clippings to be used for research**
- **The research samples would only be taken after all of the information needed by doctors diagnosing and caring for you has been obtained**

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

BCPP Summary *(Continued)*

- **The samples that you donate may be used in research now or in the future**
- **This research will run alongside your routine treatment and will not require any extra hospital visits**
- **By providing us with this information and donating samples, we hope to gather more information about the way in which bladder cancer behaves**
- **This may allow us to improve treatment in the future**

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

What do you have to do?

- **When you visit the hospital before your operation we will ….**
  - **take you through a questionnaire lasting approximately 1 hour**
  - **collect samples of your blood and urine**
- **During your operation we will collect a small sample of the bladder tissue that is removed**

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

What do you have to do? *(Continued)*

- **After your operation the we will …**
  - **send you a questionnaire and a food diary for you to fill in at home**
  - **ask you to collect samples of your toenail clippings**
- **At your first and yearly follow-up appointments there will be another 30 minute questionnaire for you to fill in**
- **We will monitor your progress over the next 5 years**

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

Do I have to take part?

- **Taking part in this study is ***entirely voluntary*****. Before you decide whether you would like to take part it is ***important*** for you to understand why the research is being done**
- **Are there any questions that you would like to ask about the study?**
- ***Informed Consent*****: once you have agreed to take part we will ask you to sign a consent form**
- **If you do decide to take part you are still free to withdraw at any time without giving a reason**
- **A decision to withdraw at any time or a decision not to take part will not affect the standard of care you receive or the relationship with any of the medical staff**

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

Possible Risks and Benefits of the BCPP Study

- **There are no ***foreseeable risks*** in taking part in this study**
- **Although there is no intended ***immediate*** clinical benefit from taking part, information obtained from this study may result in changes in the future diagnosis, treatment and follow-up of bladder cancer, and these changes may benefit you**
- ***In the future*****, if the research shows that there is a test or treatment that might be useful to you or your family, then your specialist doctor (urologist) may discuss this with you**

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

Confidentiality:

- **Your contact details, personal and medical information collected as part of this study will remain *strictly confidential***
- **All information collected will be stored at the BCPP office situated at the University of Birmingham according to the Data Protection Act 1998**
- **We will be writing to your GP to inform him/her about your participation in the trial**
- **If required, authorised professionals and members of the BCPP team may inspect your medical notes**
- **This is only for the purpose of collecting information about your treatment and ensuring that the research is carried out correctly**

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

Who Is Organising and Funding BCPP

- **BCPP is organised by** UNIVERSITY OF BIRMINGHAM
  - **Department of Public Health and Epidemiology**
  - **Cancer Research UK Institute for Cancer Studies**
- **In collaboration with the Department of Urology at the Queen Elizabeth Hospital**
- **BCPP is funded by** CANCER RESEARCH UK
- **Up to 16 NHS Trusts are taking part across the West Midlands**

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

TO BE PRINTED ON INSTITUTION HEADED PAPER

PATIENT CONSENT FORM
(Version Number 2.0, August 2009)

Title of Project: Bladder Cancer Prognosis Programme (BCPP)

Centre Name: <Name of Hospital>
Patient Identifier:
Study Number:

Name of Researcher: <Name of Urologist>

Please initial Inside the box

1. I confirm that I have read and understand the information sheet(s) dated August 2009 (Version 2.0) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason, without my medical care or legal rights being affected. ☐
3. I understand that my medical notes may be looked at by members of the BCPP research team and regulatory authority representatives, but understand that strict confidentiality will be maintained. ☐
4. I agree to take part in the above Bladder Cancer Prognosis Programme. ☐
5. I agree for samples of my bladder tissue, blood and urine and toenail clippings to be stored and used for current and future biological research projects which have received appropriate scientific and ethical approval. ☐
6. I consent to my GP being informed of my participation in this study. ☐
7. I agree for my contact details to be stored and used to contact me about aspects of the study either by telephone or by post. ☐

Name of patient (print name)	Date	Signature
Name of person taking consent	Date	Signature

(1 for patient; 1 for researcher; 1 to be kept with hospital notes)

TO BE PRINTED ON INSTITUTION HEADED PAPER

Bladder Cancer Prognosis Programme (BCPP)

Cancer Research UK Bladder Cancer Research Group

Chief Investigator:	**Dr Rik Bryan** **The University of Birmingham**
Local Investigator:	*<Name of Urologist>* *<Hospital Name>*

GENERAL PRACTITIONER INFORMATION SHEET

(Version Number 2.0, August 2009)

Dear Colleague,

Your patient ……..…. (date of birth…...../..…../…….) has been diagnosed with a bladder abnormality, which is suspected to be bladder cancer following initial clinical investigation. We have invited your patient to take part in a clinical research study. The name of this research study is the Bladder Cancer Prognosis Programme (BCPP). The study aims to examine various lifestyle, environmental and biological factors which may be associated with an increased risk of tumour recurrence or progression.

We attach a copy of the information sheet that has been given to your patient.

If you wish to obtain any further information, please contact the BCPP researcher or the local investigator (contact details are given below).

BCPP research team member: <Research Nurse/Trial Practitioner> **Tel.:** <mobile number>

Local Investigator: <Urologist> **Tel.:** <secretary's contact number>

Yours sincerely

< Local Investigator >

TO BE PRINTED ON INSTITUTION HEADED PAPER

Date Sent……../……../……..

' SELENIB' - PATIENT INFORMATION SHEET – Short Version
(Version Number 2.0, August 2009)

Chief Investigator: **Dr Rik Bryan**
University of Birmingham

Name of your Doctor: <Name of Urologist>
<Hospital Name>

A Clinical Trial Investigating the Role of **Sel**enium and Vitamin **E** in Preventing Recurrence and Progression of **N**on-Muscle-**I**nvasive **B**ladder Cancer

"SELENIB"

This shortened version of the patient information leaflet provides a brief overview of the SELENIB study. For full details please also read the full length version which will be provided to you. Thank you for taking the time to find out about the SELENIB trial.

What's the study about?
Bladder cancer is often a low-risk disease. However, for a number of patients their bladder cancer may return at some point in the future. Often, if the bladder cancer does return, it is no more serious than the original tumour, but for a number of patients the disease may become worse.

Selenium and vitamin E are important nutrients commonly found in a balanced diet. Previous clinical trials and laboratory studies have suggested that these nutrients may help guard against some cancers, including bladder cancer. There is much less known about whether these nutrients can help prevent bladder cancer from returning or getting worse once it has already developed. However, there is enough information to suggest that a large clinical trial of these nutrients is important to look into this question.

What will the study investigate?
This clinical trial will test whether supplementing your normal diet with one or both of these nutrients will reduce the chances of your bladder cancer returning or getting worse.

What will it involve?
If, after your operation (or biopsy), your doctors diagnose you with a certain type of bladder cancer, you may be eligible to participate in this study. Our researcher will discuss this with you and confirm if you meet the entry requirements. Even if you are eligible you do not have to take part if you don't want to.

If you are eligible, and if you agree to take part, we would like you to take one tablet and one soft gel capsule each day with food. The tablet will contain either the mineral supplement selenium or will only contain inactive ingredients (a “dummy” pill). The gel capsule will contain either the vitamin supplement vitamin E or will only contain inactive ingredients (a “dummy” pill). A computer will randomly select if you get the nutritional supplement or the dummy pill or one of each. You will not be told which one you have received and neither will your doctor although they can find out if they need to. **There will be a 3 out of 4 chance that you WILL receive at least one of the nutritional supplements**. Whilst taking part in the study we would ask you to let us know about any other vitamin or mineral supplements you are taking that contain either selenium or vitamin E. Taking these would not necessarily exclude you from this study but we do need to check your total doses of selenium and vitamin E to make sure that you are not taking more than the recommended level. Our researcher will calculate this for you and advise you on this.

You would need to come back to the hospital once every six months for a period of up to five years to attend a follow-up clinic with our researcher and to get the next six months treatments. To see if the levels of vitamins and minerals in your body have changed as a result of the treatment you are given, you may be asked to give a small sample of blood and a sample of your toenail clippings. If you are currently taking the anticoagulation drug ‘warfarin’, you may also need to have a few additional visits to your anticoagulation clinic.

The treatments given as part of this study are not expected to cause you any side effects as they are given at low doses and are important nutrients that are a normal part of a balanced diet. If taken at high doses, these treatments can sometimes cause side effects, the majority of which are very minor.

The treatments given as part of this study are in addition to the treatment given for your bladder condition and do not replace any part of it. When the study stops your routine bladder treatment and follow-up will continue in the normal way, although it may incorporate new discoveries or information generated by this study.

Why should I consider taking part?
There is a possibility that selenium and vitamin E may help to stop bladder cancer from coming back or getting worse. However, until a trial like this one has been completed, it is not possible to say for certain whether or not this is the case. Therefore, although we cannot promise that the study will help you, the information we will collect might help improve the treatment of patients with bladder cancer in the future.

If you are interested in finding out more about the study, please also take the time to read the full length information leaflet carefully before you make a decision about whether or not to take part. Our researcher will be happy to discuss any queries that you may have. Contact details for our researcher are given on the full length information sheet along with the contact details of someone impartial who you can talk to about the study if you wish.

If this information has interested you and you are considering taking part, please also read the full length patient information leaflet before making any decision.

TO BE PRINTED ON INSTITUTION HEADED PAPER

Date Sent……../……./…..

SELENIB - PATIENT INFORMATION SHEET

(Version Number 2.0, August 2009)

Chief Investigator: **Dr Rik Bryan**
University of Birmingham

Name of your Doctor: <Name of Urologist>
<Hospital Name>

A Clinical Trial Investigating the Role of **Sel**enium and Vitamin **E** in Preventing Recurrence and Progression of **N**on-Muscle-**I**nvasive **B**ladder Cancer

"SELENIB"

We would like to invite you to take part in the clinical trial within a programme of research called the Bladder Cancer Prognosis Programme.

Taking part in this trial is entirely voluntary. Before you decide whether you would like to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

The following information leaflet is in two parts:

- **Part 1** tells you the purpose of this study and what will happen to you if you take part
- **Part 2** gives you more detailed information about the conduct of the study.

Thank you for reading this information leaflet

1. What is the purpose of the study?

Bladder cancer is often a low-risk disease. However, for a number of patients their bladder cancer may return at some point in the future. Often, if the bladder cancer does return, it is no more serious than the original tumour, but for a number of patients the disease may become worse.

Selenium and vitamin E are important nutrients commonly found in a balanced diet. Previous clinical trials and laboratory studies have found that these nutrients may help guard against some cancers, including bladder cancer. There is much less known about whether these nutrients can help prevent bladder cancer from returning or getting worse once it has already developed. However, there is enough information to suggest that a large clinical trial of these nutrients is important to look into this question.

And so, this clinical trial will test whether supplementing your normal diet with one or both of these nutrients will reduce the chances of your bladder cancer returning or getting worse.

2. Why have I been chosen?

We would like to recruit patients who have a certain type of bladder cancer to take part in this study. Therefore, it is important that your diagnosis is confirmed before we know for sure if you are suitable to take part in this study. Your diagnosis can only be confirmed after you have had your bladder operation and the small pieces of tissue that are removed have been looked at through a microscope.

If your diagnosis **has** already been confirmed:
You have been chosen to take part because your doctor has confirmed that you have the type of diagnosis that makes you suitable for this study.

If your diagnosis has **not yet** been confirmed:
Your doctor feels that you may be suitable for the study. However, we will not know for sure until your diagnosis has been confirmed. Once your diagnosis is confirmed we will contact you to ask you if you would like to consider taking part.

In total we would like to study around 515 patients within the West Midlands region during the next 5 years.

3. Do I have to take part?

It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and will be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive or your relationship with your doctor.

4. What will happen to me if I take part?

Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments. To do this, we put people into groups and give each group a different treatment; the results are compared to see if one is better. And so, to allow us to see if there is any benefit of taking selenium and/or vitamin E supplements, we need to compare patients taking these supplements with patients taking a placebo (a placebo is a "dummy treatment", which looks like the genuine medicine but contains no active ingredient).

If you agree to take part, you will be asked to take one tablet **and** one gel capsule each day for a period of up to five years. The **tablet** will contain either selenium or inactive ingredients only (the "placebo"). The **gel capsule** will contain either vitamin E or inactive ingredients only (the "placebo"). The placebos will look and taste the same as the nutritional supplements and will contain all of the same ingredients except for the active nutrient.

You will be given **one** of the four following treatments for the length of the study:

- 1 selenium tablet + 1 vitamin E capsule daily
- 1 selenium tablet + 1 placebo capsule daily
- 1 placebo tablet + 1 vitamin E capsule daily
- 1 placebo tablet + 1 placebo capsule daily

Neither you nor your doctor will know which treatment you will be given (although, if your doctor needs to find out, he/she can do so).

To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). The results are then compared. A computer randomly selects the groups – so it's like tossing a coin to decide which treatments you receive. This process is called "randomisation". **In this way, there will be a 3 out of 4 chance that you WILL receive at least one of the nutritional supplements**.

5. What do I have to do?

You would need to take the study treatments each day for a period of up to five years. You should not take more than the specified dose. It is important that you let us know about all over-the-counter supplements you take that contain either vitamin E or selenium (e.g. multivitamins) so that we can work out that if by taking these in addition to the study treatments you would be taking more than the recommended dose. You may, however, continue taking all of your other regular medication.

Following your initial hospital visit for randomisation, you will be asked to return to the hospital every six months to see our researcher. Your study treatments will be given to you at these visits, which will continue for a period of up to five years. Our researcher will also ask you about certain aspects of your health and collect any unused tablets and capsules from you. These visits should last approximately 15 minutes. Where possible we will plan these visits to coincide with your routine bladder cancer follow-up. Prior to your first follow-up visit, a member of our research team will telephone you to see how you are getting on and to discuss any queries that you may have. At one of these follow-up visits, we may ask you to give us a sample of your toenail clippings and a small sample of your blood. This is so that we can check if the vitamin and mineral levels in your body have changed as a result of the study treatment.

By taking part in this clinical trial, you will not require any additional tests unless you are taking the drug **warfarin**. If you are already taking warfarin you will be asked to visit your anticoagulation clinic weekly for the first four weeks following the start of your treatment in this trial, after which you will just need to continue to attend your regular anticoagulation clinics as normal. If you start taking warfarin **after** starting the study treatment, you will not need to have these additional visits.

6. What will happen to the blood and nail samples taken as part of this study?

The blood and toenail samples collected as part of this study will need to be collected once only, and not all patients will need to give these samples. The samples will be used to compare the amounts of vitamin E and selenium in your body before and after starting the study treatment. After they have been collected the samples will be stored centrally, either at the University of Birmingham or at another central laboratory in the UK. The samples are stored under strict security and are given a code, so that researchers receiving the samples do not know your name or any other personal details.

7. What is the drug, device or procedure that is being tested?

Selenium and vitamin E are important nutrients commonly found in a balanced diet. Both of these nutrients are also available from pharmacies and health food shops as over-the-counter supplements and are taken regularly by many people in the UK.

Selenium:

Selenium is an essential nutrient. Most people in the UK obtain low levels of selenium from food. Selenium is naturally found in nuts, grains, meat, yeast, and some vegetables. A **low** intake of selenium has been linked to an increased risk of developing some cancers, including bladder cancer, although it is not known whether increasing the amount of selenium in your diet prevents bladder cancer from returning or getting worse once it has already developed. This is the main question that this trial intends to answer.

The selenium supplement used in this trial will be one tablet per day with a dose of 200 microgrammes.

Vitamin E:

Vitamin E (sometimes called alpha-tocopherol) is found in many foods including nuts, oils, and vegetables and people in the UK usually consume small but adequate amounts of this vitamin. Some research suggests that taking vitamin E supplements may boost the immune system and guard against the development of heart disease and some cancers, including bladder cancer. It is not known whether increasing the amount of vitamin E in your diet prevents bladder cancer from returning or getting worse once it has already developed. This is the second question that this trial intends to answer.

The vitamin E supplement used in this trial will be one capsule per day with a dose of 200 International Units.

8. What are the alternatives for diagnosis or treatment?

The treatments given as part of this trial are additional to your bladder treatment, and do not replace any part of it. If you choose not to take part in this trial, the rest of your bladder treatment will remain the same.

9. What are the side effects of any treatment received when taking part?

These nutrients are an essential part of a normal diet. **The doses of selenium and vitamin E used in this trial are not expected to cause you any side effects**, However, long term use of these supplements at higher doses have been know to cause some side effects.

Selenium:

Long-term daily use of doses much higher than the dose used in this study may lead to minor side effects which include: nausea, upset stomach, fatigue, irritability, dermatitis, cough and cold, bronchitis, hair brittleness, hair loss, bad breath, dizziness and nail tenderness. All of these side effects go away shortly after stopping taking the pills. There is no evidence to suggest that any serious side effects are caused from taking selenium supplements.

The dose used in this trial is 200 microgrammes per day. It is unlikely that you would experience any side effects from this treatment. To avoid any side effects, it is important that you let us know about any other supplements you take that contain selenium so that we can check that you are not taking more than the recommended total dose for this study.

Vitamin E:

Taking high levels of vitamin E over a long period of time may lead to minor side effects which include: diarrhoea, abdominal pain, upset stomach, blurred vision, dizziness, fatigue and weakness. All of these side effects go away shortly after stopping taking the pills. Only 1 in 200 patients taking high doses of vitamin E (2 and 4 times the dose used in this trial) stopped taking vitamin E because of these side effects. The lower dose of vitamin E used in this trial is not expected to cause such side effects.

A recent study looked at the evidence for and against taking vitamin E supplements. This study included over 130,000 patients from 19 separate trials using a wide range of vitamin E doses for at least one year. Results suggested that there was a very small increase in the risk of death in the group taking daily vitamin E in doses **higher than** 400 International Units (IU), compared with the group taking a 'placebo'. This increased risk was 4% above the normal death rate during an average follow-up period of four years. However, doses **lower than** 400 IU did not appear to either increase or decrease the risk of death. **There is no evidence to suggest that the dose of vitamin E used in this trial, 200 IU per day, is associated with this effect.**

For Women:

Large studies have demonstrated that during pregnancy there are no risks to a mother or an unborn child associated with taking either selenium or vitamin E supplementation. However, patients who are pregnant are excluded from this study, and so you should inform us if you become pregnant or whether you are trying to conceive.

10. What if I already take these supplements?

In order to conduct our trial properly, and to avoid patients having side effects from taking too much of these supplements, it is essential that patients involved in this trial let us know about all multivitamins and other supplements that contain selenium and/or vitamin E that they are taking in addition to their study treatment. We will check the doses and let you know if it is ok for you to continue with your study treatment. Please speak to our researcher if you have any concerns about this or if you are unsure whether your multivitamin contains either selenium or vitamin E.

11. What are the other possible disadvantages and risks of taking part?

As discussed above, apart from a small chance of experiencing the side-effects mentioned above, there are no clear risks of taking part in this study.

If you have private medical insurance you may wish to consult your medical insurers before agreeing to take part in the study. This is to ensure that you participation will not affect your medical insurance cover, although this is unlikely.

12. What are the possible benefits of taking part?

There is a possibility that selenium and vitamin E may help to stop bladder cancer from coming back or getting worse. However, until a trial like this one has been completed, it is not possible to say for certain whether or not this is the case. Therefore, although we cannot promise that the study will help you, the information we will collect might help improve the treatment of patients with bladder cancer in the future.

13. What happens when the research study stops?

At the end of the study period (up to five years) and once you have finished the study treatment, we will give you a telephone number to contact if you would like to find out which of the four treatment combinations you have received. The four treatment combinations are the ones listed in section 6 of this information leaflet.

When the study stops your routine bladder cancer treatment and follow-up will continue in the normal way, although it may incorporate new discoveries or information generated by this study.

If this study suggests that these nutritional supplements are of benefit, you will be informed by your Urologist. He/she will discuss these findings with you and they may recommend that you take these widely available supplements.

14. **What if there is a problem?**

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

15. **Will my taking part in the study be kept confidential?**

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

16. **What if I have other concerns or would like further information?**

If you have any concerns or other questions about this study or the way it has been carried out, you should contact your Urologist or the BCPP researcher at your hospital – details listed below. . If you would like advice from someone independent of the study concerning your participation, you should contact <e.g. Urology CNS>.

Contact Details:

BCPP research team member: <Research Nurse/Trial Practitioner> **Tel.:** <contact number>

Local Investigator: <Urologist> **Tel.:** <secretary's contact number>

This completes Part 1 of the Information Sheet.
If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

17. **What if relevant new information becomes available?**

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your Urologist will tell you about it and discuss whether you want to or should continue in the study. If you decide not to carry on, your Urologist will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your Urologist might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

18. **What will happen if I don't want to carry on with the study?**

As mentioned in part 1 of this information sheet, your participation in this study is entirely voluntary and you are free to withdraw at any time. You may wish to only withdraw from treatment, but may still be willing to attend the regular follow-up visits. Alternatively, you may wish to withdraw entirely (ie: withdraw from treatment and follow-up). In such an event we may still use the data collected up to your withdrawal and we may, with your permission, collect further follow-up information about you from the NHS Central Register (NHSCR) or the Office for National Statistics (ONS).

19. **What if there is a problem?**

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. In such cases please contact <Name local PI> <PI contact number>. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action for compensation against the research sponsor (University of Birmingham) or the NHS Trust where you received treatment, but you may have to pay your legal costs. Regardless of this, if you wish to complain, or have any concerns during the course of this study, the normal National Health Service complaints mechanism is available to you.

20. **Will my taking part in this study be kept confidential?**

All information which is collected about you during the course of the research will be kept strictly confidential. If you agree to take part in this study we will need you to sign a consent form. You will be given a copy of the consent form and this information sheet to keep.

With your consent, we will be informing your GP about your participation in this study. If you are currently taking warfarin, we will also notify your anticoagulation specialist. Authorised professionals, other than those involved directly in your care, may inspect your medical notes. Information contained within your medical notes would be used only for the purposes of collecting information about your treatment and to check that the research is being carried out correctly. These authorised professionals include members of the BCPP (Bladder Cancer

Prognosis Programme) research team and regulatory authority representatives. We may also wish to obtain further follow-up information about you from the National Health Service Care Register (NHSCR) and the Office for National Statistics (ONS).

Information on all patients entered into this study will be sent to the BCPP Study Office which is located at The University of Birmingham where it will be retained in secure storage and handled according to the 1998 Data Protection Act. It may be necessary to provide your name or other identifiable information to the NHSCR or the ONS in the future for the purposes of follow up. Limited clinical information may be passed on to researchers within or outside of the UK. Some countries outside Europe may not have laws which protect your privacy to the same extent as the Data Protection Act in the UK or European Law. However, it would not be possible to identify any patient from the information.

21. **What will happen to the results of the research study?**

Important results from the study will be published as they become available, which may be during the course of the study or after the study has finished, and this could possibly take several years. We intend that any results will be published in peer-reviewed journals or will be presented at meetings involved with this field of cancer research, and these publications will be available upon request from your Urologist. You will not be identified in any report or publication.

22. **Who is organising and funding the research?**

The research is being organised by The Department of Public Health and Epidemiology at The University of Birmingham, in collaboration with the Cancer Research UK Institute for Cancer Studies at The University of Birmingham, The Department of Urology at The Queen Elizabeth Hospital, Birmingham, and all participating Urology Departments within the West Midlands. The research is funded by Cancer Research UK. The doctors conducting this study are not being paid for including and looking after you within this study.

23. Who has reviewed the study?

This study has been reviewed by the Trent Multi-centre Research Ethics Committee, The UK Medicines and Healthcare Products Regulatory Authority (MHRA) and by scientific experts at Cancer Research UK.

Finally, thank you for taking the time to read this information sheet and for taking part in the study, if you agree to do so.

Date Sent……../……./…..

Addendum *1.0*, *November 2011* to
Patient Information Sheet version *2.0, August 2009*

A Clinical Trial Investigating the Role of Selenium and Vitamin E in Preventing Recurrence and Progression of Non-Muscle-Invasive Bladder Cancer
"SELENIB"

This Addendum to Patient Information Sheet version *2.0* provides new information regarding the follow-up procedures that will take place once the SELENIB trial has ended. This is an addition to the Patient Information Sheet that you have already consented to. The changes are as follows:

24. **What will happen when the trial ends?**

When you have finished taking your final treatment packs, you will attend your final follow-up meeting with your local SELENIB Research Nurse as normal. After this, the clinician assigned to your care will continue your follow-up in accordance with their normal practice. Some of the research nurses at your local hospital are part of local and national networks of research staff and they will continue to monitor your progress via your hospital records, although after your final follow-up meeting, you will not see the SELENIB Research Nurses in the same regular fashion as before. Once you have finished taking the medication, further follow-up data may be collected after from your medical notes, the NHS central register (NHSCR), the Office for National Statistics (ONS) and the West Midlands Cancer Intelligence Unit (WMCIU).

25. **Update on published findings from the SELECT clinical trial**

You may also have seen recent reports in the press and on TV about the "SELECT" trial in the USA and Canada. SELECT was a trial of selenium (200 micrograms per day) and vitamin E (400 International Units per day), investigating whether either compound could prevent the development of prostate cancer. The study involved over 35,000 healthy men over 50-years of age, who took the trial treatments for over 5-years. This study ended early because an analysis of the data in October 2008 showed that there was no clear benefit of either compound in preventing prostate cancer. The SELECT researchers continued to follow-up these patients for another 2-years, and have recently published results that suggest that there is a small (1.1%) increased risk of developing prostate cancer in the patients taking vitamin E alone – for every 1000 men taking part in the study, there were 11 extra cases of prostate cancer in patients taking vitamin E only when compared to those taking the dummy pill ("placebo").

Because SELENIB also involves vitamin E, we considered the results of the SELECT trial very carefully. We also have a duty to inform you of the results of this trial.

Firstly, it is important to highlight that the SELECT trial is just one study, and several other studies have **not** shown the same results: other studies have actually demonstrated health benefits for patients taking vitamin E, including a reduced risk of developing prostate cancer. Myself and the rest of the SELENIB researchers (including our Independent Monitoring Committee) are not concerned about the results of the SELECT trial (which only seem to be relevant to men). This is because:

- **The dose of vitamin E that we are using in SELENIB is 200 International Units per day, half the dose used in the SELECT trial.**
- **Most patients will have been taking part in SELENIB for much less than 4-years.**
- **The participants in SELECT were all normal healthy men taking part in the trial to prevent prostate cancer, whereas SELENIB participants are all patients being treated for bladder cancer where there is information to suggest that both vitamin E and selenium may be helpful.**

We therefore consider that it is safe to finish your last SELENIB treatment pack, but if you would prefer not to then that is OK – please inform your SELENIB trial nurse of this decision. Should you be concerned about prostate cancer as a result of taking part in SELENIB, then your GP or the Urologist who is looking after you for bladder cancer will be able to advise you further.

All other aspects of the previous Patient Information Sheet version number *2.0*, which you have already consented to, will remain in effect.

Informed Consent Form for Addendum *1.0, November 2011* to
Patient Information Sheet version *2.0, August 2009*

A Clinical Trial Investigating the Role of **Sel**enium and Vitamin **E** in Preventing Recurrence and Progression of **N**on-Muscle-**I**nvasive **B**ladder Cancer
"SELENIB"

Centre: ..... **Study Number:** ☐☐☐☐

Patient Identifier: ☐☐☐☐☐

Principal Investigator: ..... **Trial Reference Number: 2005-003021-19**

Please tick Yes or No for each of the following statements:	Yes	No
I confirm I have been informed about the SELECT Trial results.	☐	☐
I agree to continue participating in the SELENIB trial.	☐	☐
I confirm that I have read and understand the addendum and agree to the long-term follow-up care I will receive.	☐	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.	☐	☐

_____	_____	_____
Name of patient	**Date**	**Signature**
_____	_____	_____
Name of person taking consent	**Date**	**Signature**

You must have signed the
Site Signature & Delegation Log

NOTE: This flipchart is to be used as a discussion guide during the informed consent process, in addition to the printed Patient Information Sheet, to ensure that study information is clearly and accurately presented both verbally and in writing.

Bladder Cancer Prognosis Programme
"BCPP"

"SELENIB" Trial

Patient Information Flip-Chart

UNIVERSITY OF BIRMINGHAM

CANCER RESEARCH UK

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

"SELENIB" Introduction

- We would like to invite you to take part in a clinical trial called "SELENIB"
- The SELENIB trial is a part of the Bladder Cancer Prognosis Programme (BCPP) which you **may also** currently be participating in
- Taking part in this trial is entirely **voluntary**
- Before you decide whether you would like to take part it is important for you to **understand** why the research is being done

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

What is a 'trial'?

- Sometimes we don't know which way of treating patients is best
- To find out we often need to **compare** different treatments
- We do this by randomly **allocating** patients into groups and give each group a **different** treatment
- The results are then **compared** to see if one is better than the other

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

What is the trial about?

- Bladder cancer is often a **low risk** disease, however for a number of patients their bladder cancer may return at some point in the future
- Often if the bladder cancer does return, it is no more serious than the original tumour, but for a number of patients the disease may become worse
- **Selenium and vitamin E** are important nutrients commonly found in a balanced diet. Previous studies have found that these nutrients may help guard against some cancers, including bladder cancer
- However, it is not yet known if these nutrients can help prevent bladder cancer from returning or getting worse once it has already developed
- There is enough information to suggest that a large clinical trial of these nutrients is important to look into this question

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

What are we studying?

This clinical trial will **test** whether supplementing your normal diet with one or both of the nutrients, **selenium** and **vitamin E**, will reduce the chances of your bladder cancer returning or getting worse

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

Why have you been chosen?

- For this trial we would like to study around 515 patients/volunteers across the West Midlands
- If, after your operation (or biopsy), your doctors diagnose you with a certain type of bladder cancer, you **may** be eligible to participate in this study
- We will **discuss** this with you and confirm if you meet the entry requirements
- Even if you are **eligible** you do not have to take part if you do not want to. If you decide not to take part, this will not affect the treatment that you receive or your relationship with any of the medical staff

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

What will it involve?

- If you are eligible, and if you agree to take part in the "**SELENIB**" trial, we would like you to take **one tablet** and **one gel capsule** each **day** with food for up to five years
  - The tablet will contain either the nutritional supplement **selenium** or will contain ***inactive*** ingredients only (a "**dummy**" pill)
  - The gel capsule will contain either the nutritional supplement **vitamin E** or will contain **inactive** ingredients only (a "**dummy**" pill)
- A computer will randomly select whether you will get the nutritional supplements or the 'dummy' pills or one of each. This process is called **randomisation**
- There will be a three out of four chance that you will receive at least one of the nutritional supplements
- You will not be told which treatment you have been allocated and neither will your doctors or nurses although they can find out if they need to

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

What do you have to do?

- Following your initial hospital visit for **randomisation** you will be asked to return to the hospital to see a member of our research team every **six *months*** for a period of up to **five years**
- **These visits should coincide with your routine follow-up visits where possible**
- At these visits we will ask you about certain aspects of your health and collect from you any unused tablets and give you your next six months supply of study treatments
- By taking part in this clinical trial, you will **not** require any additional tests
- However, if you are already taking the drug "**warfarin**" you will be asked to visit your anticoagulation clinic weekly for the first four weeks following the start of your study treatment. This will not be necessary if you start taking warfarin in the future

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

What do you have to do? (continued)

- You may be asked to give a small sample of your blood and/or toenail clippings after you have been taking the treatment for a period of time
- This is so that we can compare the amount of selenium and vitamin E that you have in your body after you have started taking the treatment with the levels that were there before you started taking the treatment
- Not all patients will be asked to give these samples. Our researcher will discuss this with you if appropriate
- For your safety and to conduct our study properly, we would ask you **not to take** any other vitamin or mineral supplements that contain **more than** 200mcg selenium and 100IU vitamin E per day
- **You may however continue taking all of your other regular medication**

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

Who else will have access to my information?

- If you agree to take part, information collected about you will be treated with strict confidentiality
- With your **consent** we will write to your GP to inform him/her about your participation in the 'SELENIB' trial
- To ensure that the trial is being carried out correctly, authorised professionals and members of the BCPP team may inspect your medical notes
- In the future, to help us obtain follow-up information about you, it may be necessary to provide your details to the National Health Service Care Register (NHSCR) or the Office for National Statistics (ONS). This would only be done with your **consent**
- Important results during or after the study will be published as they become available, it is **important** for you to know that you will **not be identified** in any report or publication

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

Are there any side effects?

- The treatments given as part of this study are **not expected** to cause you any side effects as they are important nutrients that are a **normal** part of a balanced diet and will be given at **low doses**
- If taken at **high doses**, these treatments can sometimes cause side effects, the majority of which are only minor. Full details are given in the patient information leaflet
- Please speak to our researcher if you have any worries about taking these supplements
- He/she will be happy to go through the patient information leaflet with you and discuss any concerns
- At this point, are there **any questions** that you would like to ask about the study?

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

Why should I consider taking part?

- There is the possibility that selenium and vitamin E **may help prevent** bladder cancer from returning or getting worse
- However, until a trial like this has been completed, we cannot promise that the study will benefit you
- The information we will collect may help improve the treatment of patients with bladder cancer **in the future**

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

What happens next?

- We would like you to keep the patient information sheet provided, so that you can read it carefully and discuss it with others if you wish
- Ask us if there is anything that is not clear or if you would like more information. Take time to decide if you want to take part
- We will let you know whether you meet the entry requirements and if so, will ask you if you would like to participate
- **If you do decide** to take part we will ask you to see a member of our team to sign a consent form and to collect your first six months supply of study treatments from the hospital pharmacy
- After that we would like to see you at the hospital every six months during the next five years to check how you are doing, collect any unused tablets and to give you your next six months supply of treatments

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

Many thanks

For taking the time to find out about the SELENIB trial and taking part in the trial, if you agree to do so

Bladder Cancer Prognosis Programme
Flip-chart, Version 2.0 August 2009

TO BE PRINTED ON INSTITUTION HEADED PAPER

'SELENIB' TRIAL - PATIENT CONSENT FORM

(Version Number 2.0, August 2009)

Title of Project: A Clinical Trial Investigating the Role of **Sel**enium and Vitamin **E** in Preventing Recurrence and Progression of **N**on-Muscle-**I**nvasive **B**ladder Cancer (**SELENIB**)

Centre Name: <Name of Hospital>
Patient Identifier:
Study Number:

Name of Researcher: <Name of Urologist>

Please initial inside the box

1. I confirm that I have read and understand the information sheet(s) dated August 2009 (Version 2.0) for the above trial and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason, without my medical care or legal rights being affected. ☐
3. I agree to take part in the above SELENIB clinical trial. ☐
4. I understand that my medical notes may be looked at by members of the BCPP research team and regulatory authority representatives, but understand that strict confidentiality will be maintained. ☐
5. I understand that I may be asked to give a small sample of my blood and/or a sample of my toenail clippings for the purposes of checking the levels of selenium and vitamin E in my body. ☐
6. I understand that information about me may be sent to or requested from the NHS Central Register and the Office for National Statistics for the purposes of follow-up and that anonymous information about me may be passed to researchers in other countries having a lower standard of Data Protection than the UK. ☐
7. I consent to my GP, and where necessary my anticoagulation doctor, being informed of my participation in this study. ☐

Name of patient (print name)	Date	Signature
Name of person taking consent	Date	Signature

(1 for patient; 1 for researcher; 1 to be kept with hospital notes)

TO BE PRINTED ON INSTITUTION HEADED PAPER

Date Sent…...../……../……...

SELENIB CLINICAL TRIAL
GENERAL PRACTITIONER INFORMATION SHEET
(Version Number 2.0 August 2009)

Chief Investigator: **Dr Rik Bryan**
University of Birmingham

Local Investigator: <Name of Urologist>
< Hospital Name>

Dear Colleague,

Your patient …… (date of birth …...../……..…/…….) has been given information about a phase III clinical trial entitled 'SELENIB' for which they may be eligible to be part of. The SELENIB trial is a double-blind, placebo-controlled, randomised controlled trial which aims to examine whether the nutritional supplements, selenium and vitamin E can help prevent the recurrence or progression of non-muscle-invasive bladder cancer. If your patients' pathology confirms that they have non-muscle-invasive bladder cancer, they will be invited to participate in the study. If they agree, they will be randomised to receive one of the following treatment arms:

- 200mcg selenium tablet and 200IU vitamin E gel capsule
- 200mcg selenium tablet and placebo gel capsule
- placebo tablet and 200IU vitamin E gel capsule
- placebo tablet and placebo gel capsule

They will be required to take the allocated treatment daily for a period of up to 5 years. Full details of the trial are provided for your information in the attached copy of the patient information leaflet. If you wish to obtain any further information, please contact our BCPP researcher or the local investigator (contact details are given below).

BCPP research team member: <Research Nurse/Trial Practitioner> **Tel.:** <contact number>

Local Investigator: <Urologist> **Tel.:** <secretary's contact number>

Yours sincerely

< Local Investigator >

APPENDIX 2
NON ELIGIBLE PATIENT LETTERS (Version 2.0, August 2009)

NOTE: TO BE SENT TO PATIENTS RECRUITED INTO BCPP, WHO DO NOT RECEIVE A PATHOLOGICAL DIAGNOSIS OF BLADDER CARCINOMA.

TO BE PRINTED ON HOSPITAL LETTERHEADED PAPER.

<Patient Title> <Patient Surname>
<Patient Address 1>
<Patient Address 2>
<Patient Address 3>
<Patient Address 4>
<Patient Address 5>
<Patient Post Code>

Date Sent…../…../…..

Dear <Patient Title> <Patient Surname>

RE: Bladder Cancer Prognosis Programme (BCPP)

Thank you very much for agreeing to participate in the research study called "BCPP".

As discussed at our first meeting, this research study involves patients who have a specific type of bladder abnormality. As explained in the BCPP Patient Information Sheet, some patients will not have this type of abnormality and so will not be required to continue their participation in the study after their operation.

I have heard from your doctor that your diagnosis has been confirmed and that you have been contacted and given this information. The type of condition that you have been diagnosed with means that you are not eligible to participate further in the BCPP study.

Therefore, we will not need to collect any further information or samples from you (including toenail clippings) as part of this research study, and we will not ask you to fill in the food diary or any further questionnaires.

The samples you have already donated to the BCPP tissue bank and the information that you have given continues to be valuable to our research.

Please contact me if you have any further questions about the research.

Thank you once again for your contribution.

Yours sincerely

<Signature of local BCPP researcher>

<Name of BCPP Researcher> **Tel.:** <contact number>

NOTE: TO BE SENT TO PATIENTS GIVEN THE SELENIB PATIENT INFORMATION LEAFLET WHO DO NOT RECEIVE A PATHOLOGICAL DIAGNOSIS OF NON-MUSCLE-INVASIVE TCC.

TO BE PRINTED ON HOSPITAL LETTERHEADED PAPER

<Patient Title> <Patient Surname>
<Patient Address 1>
<Patient Address 2>
<Patient Address 3>
<Patient Address 4>
<Patient Address 5>
<Patient Post Code>

Date Sent…../…../…..

Dear <Patient Title> <Patient Surname>

RE: Selenium and Vitamin E trial 'SELENIB'

Thank you very much for taking the time to find out about the SELENIB trial.

As discussed at our last meeting, the SELENIB trial involves patients who have a specific type of bladder abnormality. As explained in the SELENIB Patient Information Leaflet, some patients will not have this type of abnormality and so will not be asked to take part in the trial after their operation.

I have heard from your doctor that your diagnosis has been confirmed and that you have been contacted and given this information. The type of condition that you have been diagnosed with means that you are not eligible to participate in the SELENIB trial. Therefore, your bladder treatment and follow-up will continue in the normal way and you will not be required to take the additional vitamin and mineral supplements.

If you are taking part in the Bladder Cancer Prognosis Programme (BCPP), we would like you to continue to participate as normal (unless our researcher tells you otherwise or you decide you don't want to). This means that we would still like to continue collecting information from you including a food diary and questionnaires and samples of your toenail clippings. We would also like to continue to monitor your progress at your hospital follow-up visits.

Please contact me if you have any further questions about the research.

Thank you once again for your contribution.

Yours sincerely

<Signature of local BCPP researcher>

<Name of BCPP Researcher> **Tel.:** <contact number>

APPENDIX 3
BASELINE, POSTAL AND FOLLOW-UP QUESTIONNAIRES

- **Initial Questionnaire**
  (Completed at diagnosis)

- **Postal Questionnaire**
  (Posted to the patient at the time of the first follow-up, returned by post from the patient

- **Food and Micturition Diary**
  (Posted to the patient at the time of the first follow-up, returned by post from the patient

- **Follow-up Questionnaire**
  (Completed at the time of the first follow-up and annual follow-ups thereafter)

Study Number: ☐☐☐☐

BLADDER CANCER PROGNOSIS PROGRAMME

Cancer Research UK Bladder Cancer Group

Initial

Questionnaire

CONFIDENTIAL

VERSION: FINAL 1.0 November 2005

PLEASE DESTROY PREVIOUS VERSIONS

A programme of research

Conducted by: *Funded by:*

UNIVERSITY OF BIRMINGHAM

CANCER RESEARCH UK

INTRODUCTION

In order to provide better health care for bladder cancer patients, we hope to discover more about how bladder cancer is related to people's circumstances. We are particularly interested in what we can do to prevent bladder cancers from coming back after they have been treated.

The questions that you will be asked will include questions about your lifestyle, your behaviours, your health and the help and support you receive from the people around you.

There may be some questions that you think are unusual. The questions are not used to test you in any way and the responses that you give will not be used to make any judgements of you. There are no right or wrong answers. All of your responses will be treated as strictly confidential and will be used only for medical research.

Some of the questions ask for personal information. If you feel that any of the questions are too personal, do not answer them. However, by answering these questions, you will help us to discover links between lifestyles and health.

I <Name of researcher> will take you through each question and keep a record of your responses. There is no time limit, so if you want a little time to think about any of the questions please do so. Try to answer every question even if the answer is 'I can't remember' or 'I don't know'.

If you have any other questions, or if there is anything that you feel you don't understand please ask me < (Name of researcher) > at any time.

Thank you for taking the time to participate in this study.

CANCER RESEARCH UK	**BLADDER CANCER PROGNOSIS PROGRAMME (BCPP)**	INITIAL QUESTIONNAIRE **PERSONAL DETAILS** SECTION 1:

Patient Identifier: *First 3 letters from surname followed by first 2 letters from forename*			☐☐☐☐☐ *e.g. John Smith = SMIJO*
Date of Birth: Sex: *(Please circle)*	D D M M Y Y Y Y **M F**	Responsible Urologist: Hospital No:	_____ _____
Date of Interview: Time of Interview *(24hour)*	D D M M Y Y Y Y ☐☐ : ☐☐	Name of Interviewer: Hospital Name:	_____ _____
Will the interview take place with the support of a translator			Yes ☐ No ☐

Section		Completed by? Patient	Nurse	Date Completed? *(dd/mm/yyyy)*
1	General Information	☐	☐	||||||||
2	Smoking Behaviours	☐	☐	||||||||
3	Dietary Behaviours	☐	☐	||||||||
4	Other Behaviours	☐	☐	||||||||
5	Medications	☐	☐	||||||||
6	Medical History	☐	☐	||||||||
7	Social Support	☐	☐	||||||||
8	General Health	☐	☐	||||||||

SECTION 1: CONTACT DETAILS

1.1. What is your current postal address?

House number and street	
Location (Town/City)	
County	
Country	
Postcode (if known)	

1.2. What is your current home telephone number? *(Including dialling code)* ☐☐☐☐☐-☐☐☐☐☐☐☐

1.3. What is your current mobile telephone number, if you have one? ☐☐☐☐☐☐☐☐☐☐☐

CANCER RESEARCH UK	**BLADDER CANCER PROGNOSIS PROGRAMME (BCPP)**	INITIAL QUESTIONNAIRE **GENERAL INFORMATION** SECTION 2:

SECTION 2: GENERAL INFORMATION

2.1. What is the name of your GP? Dr. ☐

2.2. What is the name of you GP practice? ☐

2.3. What is the practice address?

Number and street name ☐

Location (Town/City) ☐

Postcode (if known) ☐

GP Phone Number (if known) ☐☐☐☐☐-☐☐☐☐☐☐☐

MARITAL STATUS

2.4. What is your current marital status? (tick appropriate box)

Single ☐ Married / living with partner ☐ Widowed ☐ Separated ☐ Divorced ☐

ETHNIC ORIGIN

2.5. To which of these groups do you consider you belong to? (tick appropriate box)

White ☐ Black, Caribbean ☐ Black, other ☐ Chinese ☐ Pakistani ☐

Indian ☐ Bangladeshi ☐ Other ☐ 'Other' specify _____

EDUCATION AND QUALIFICATIONS

2.6. How old were you when you left school? ☐☐

2.7. Do you have any of the following qualifications? *(Tick all applicable)*

School Leaving Certificate	☐	Technical College Exams / City & Guilds	☐	Trade Certificates	☐
GCE "O" LEVEL or GCSE	☐	Completed Apprenticeship	☐	Teaching Diploma, HNC	☐
CSE	☐	Higher National Diploma (HND)	☐	Secretarial College Exams	☐
"A" Level, Highers	☐	Matriculation (University entry exam)	☐	University Degree	☐
Other	☐	*'Other' describe:* _____			
None	☐				

SECTION 3: SMOKING BEHAVIOUR

When completing the following questions, please indicate your **CURRENT** smoking behaviours

When answering these questions, the term 'Never smoked' means that you have never smoked **or** have smoked on less than ten occasions during your lifetime.

3.1. Do you currently smoke any form of tobacco? *(tick appropriate box)*

Yes	☐	*Please complete **PARTS A and B.***
No, but I used to smoke	☐	*Please complete **PARTS A and B.***
No, I have never smoked	☐	*Please complete **PART B** only.*

PART A – This section is to be completed by current and ex-smokers only.

FILTER CIGARETTES

3.2. Do you currently smoke filter cigarettes? *(tick appropriate box)*

Yes	☐	***Go to question 3.5***
No, but I used to smoke filter cigarettes	☐	***Go to question 3.3***
No, I have never smoked filter cigarettes	☐	***Go to question 3.10***

3.3. How old were you when you stopped smoking filter cigarettes completely? ☐☐ *Years old*

3.4. How old were you when you stopped smoking filter cigarettes regularly? ☐☐ *Years old*

3.5. How old were you when you started smoking filter cigarettes? ☐☐ *Years old*

3.6. How old were you when you started smoking filter cigarettes daily? ☐☐ *Years old*

Never smoked daily ☐

3.7. How many filter cigarettes do/did you smoke on average per week? ☐☐☐

3.8. What brand of filter cigarettes do/did you usually use? _____

3.9. How deep do/did you usually inhale the smoke? *(tick appropriate box)*

Mouth only	☐
Throat	☐
Lung	☐

SMOKING BEHAVIOUR *(Continued)*

NON FILTER CIGARETTES

3.10. Do you currently smoke non filter cigarettes*? (tick appropriate box)*

- Yes ☐ ***Go to question 3.13***
- No, but I used to smoke non filter cigarettes ☐ ***Go to question 3.11***
- No, I have never smoked non filter cigarettes ☐ ***Go to question 3.18***

3.11. How old were you when you stopped smoking non-filter cigarettes completely? ☐☐ *Years old*

3.12. How old were you when you stopped smoking non-filter cigarettes regularly? ☐☐ *Years old*

3.13. How old were you when you started smoking non-filter cigarettes? ☐☐ *Years old*

3.14. How old were you when you started smoking non-filter cigarettes daily? ☐☐ *Years old*

Never smoked daily ☐

3.15. How many non filter cigarettes do/did you smoke on average per week? ☐☐☐

3.16. What brand of non filter cigarettes do/did you usually use? _____

3.17. How deep do/did you usually inhale the smoke? *(tick appropriate box)*

- Mouth only ☐
- Throat ☐
- Lung ☐

HAND ROLLED CIGARETTES

3.18. Do you currently smoke hand-rolled cigarettes? *(tick appropriate box)*

- Yes ☐ ***Go to question 3.21***
- No, but I used to smoke hand-rolled cigarettes ☐ ***Go to question 3.19***
- No, I never smoked hand-rolled cigarettes ☐ ***Go to question 3.25***

3.19. How old were you when you stopped smoking hand-rolled cigarettes completely? ☐☐ *Years old*

3.20. How old were you when you stopped smoking hand-rolled cigarettes regularly? ☐☐ *Years old*

3.21. How old were you when you started smoking hand-rolled cigarettes? ☐☐ *Years old*

SMOKING BEHAVIOUR *(Continued)*

HAND-ROLLED CIGARETTES *(Continued)*

3.22. How many hand-rolled cigarettes do/did you smoke on average per week? ☐☐☐

3.23. What brand of hand-rolled cigarettes do/did you usually use? _____

3.24. How deep do/did you usually inhale the smoke? *(tick appropriate box)*

- Mouth only ☐
- Throat ☐
- Lung ☐

CIGARS

3.25. Do you currently smoke cigars? *(tick appropriate box)*

- Yes ☐ ***Go to question 3.28***
- No, but I used to smoke cigars ☐ ***Go to question 3.26***
- No, I have never smoked cigars ☐ ***Go to question 3.32***

3.26. How old were you when you stopped smoking cigars completely? ☐☐ *Years old*

3.27. How old were you when you stopped smoking cigars regularly ☐☐ *Years old*

3.28. How old were you when you started smoking cigars? ☐☐ *Years old*

3.29. How many cigars do/did you smoke on average per week? ☐☐☐

3.30. What brand of cigars do/did you usually use? _____

3.31. How deep do/did you inhale the smoke? *(tick appropriate box)*

- Mouth only ☐
- Throat ☐
- Lung ☐

PIPE

3.32. Do you currently smoke a pipe? *(tick appropriate box)*

- Yes ☐ ***Go to question 3.35***
- No, but I used to smoke a pipe ☐ ***Go to question 3.33***
- No, I have never smoked a pipe ☐ ***Go to question 3.39***

SMOKING BEHAVIOUR *(Continued)*

PIPE *(Continued)*

3.33. How old were you when you stopped smoking a pipe completely? ☐☐ *Years old*

3.34. How old were you when you stopped smoking a pipe regularly? ☐☐ *Years old*

3.35. How old were you when you started smoking a pipe? ☐☐ *Years old*

3.36. How many pipes do/did you smoke on average per week? ☐☐☐

3.37. What brand of tobacco do/did you usually use in your pipe? _____

3.38. How deep do/did you usually inhale the smoke? *(tick appropriate box)*

- Mouth only ☐
- Throat ☐
- Lung ☐

PART B – This section is to be completed by all patients

PASSIVE SMOKING

3.39. During your childhood (before you were 18), did you live with someone who smoked? *(tick appropriate box)*

- Yes ☐
- No ☐ ***Go to question 3.41***

3.40. For how many years did you live with smokers during your childhood? ☐☐ *Years*

3.41. During your adult life (after you were 18), have you lived with someone who smoked? *(tick appropriate box)*

- Yes ☐
- No ☐ ***Go to question 3.44***

3.42. For how many years did you live with smokers during your adulthood? ☐☐ *Years*

3.43. What was the usual duration of your exposure? ☐☐ *Hours per day*

3.44. Have you ever been exposed during your indoor work to co-workers who smoked in the same room? *(tick appropriate box)*

- Yes ☐
- No, not exposed indoors ☐ ***Go to question 3.47***
- No, I have never worked indoors ☐ ***Go to question 3.47***

3.45. For how many years have you been exposed to smoking co-workers indoors? ☐☐ *Years*

3.46. What was the usual duration of your exposure? ☐☐ *Hours per day*

3.47. How frequently are you exposed to other people's tobacco smoke in public places (e.g. shopping, restaurants, bars) for a minimum of 5 consecutive minutes?

☐☐ *Times per week*

SECTION 4: DIETARY BEHAVIOURS

The questions in this section ask about your normal diet during the last year

4.1. Please indicate how often on average, **during the past year**, you have eaten each of the food types that are listed below

	Average Use Last Year					
	Never or less than once per month	1-3 per month	Once a week	2-4 per week	5-6 per week	At least once per day
STAPLE FOODS						
Bread ……..	☐	☐	☐	☐	☐	☐
Potatoes……..	☐	☐	☐	☐	☐	☐
Pasta……. (eg. Macaroni, Spaghetti)	☐	☐	☐	☐	☐	☐
Rice ……	☐	☐	☐	☐	☐	☐
Noodles……..	☐	☐	☐	☐	☐	☐
Wheat …… (eg. Whole grain bread)	☐	☐	☐	☐	☐	☐
Cereal…….. (eg. Oats, bran, corn)	☐	☐	☐	☐	☐	☐
MEAT						
Meat (no organs)…… (eg. Pork, Steak, Beef, Lamb)	☐	☐	☐	☐	☐	☐
Organ Meat……. (eg. Liver, Heart, Kidney)	☐	☐	☐	☐	☐	☐
Chicken……	☐	☐	☐	☐	☐	☐
Other Poultry…….. (eg. Goose, Duck, Pigeon)	☐	☐	☐	☐	☐	☐
FISH						
Dark Fleshed Fish……. (eg. Mackerel, Salmon, Anchovies, Sardines, Trout, Tuna, Herring)	☐	☐	☐	☐	☐	☐
White fleshed fish ……. (eg. Cod, Haddock, Hake, Halibut, Plaice, Seabass, Skate, Sole)	☐	☐	☐	☐	☐	☐
Seafood…… (eg. Prawn, Crab, Lobster, Cockles, Winkles, Squid, Octopus, Mussels)	☐	☐	☐	☐	☐	☐
VEGETABLES						
Fruit Vegetables……... (eg. Tomato, Cucumber, Aubergine)	☐	☐	☐	☐	☐	☐

DIETARY BEHAVIOURS

	Average Use Last Year					
	Never or less than once per month	**1-3 per month**	**Once a week**	**2-4 per week**	**5-6 per week**	**At least once per day**
VEGETABLES *(Continued)*						
Flower vegetables…… (eg. Broccoli, Cauliflower)	☐	☐	☐	☐	☐	☐
Leafy vegetables…… (eg. Spinach, Cabbage, Lettuce)	☐	☐	☐	☐	☐	☐
Stem vegetables…… (eg. Asparagus, Celery, Fennel)	☐	☐	☐	☐	☐	☐
Mushrooms……	☐	☐	☐	☐	☐	☐
Bulbs…… (eg. Onion, Garlic, Leek, Shallot)	☐	☐	☐	☐	☐	☐
Roots…… (eg. Beetroot, Swede, Carrot, Parsnip)	☐	☐	☐	☐	☐	☐
FRUIT						
Citrus Fruits…… (eg. Orange, Lemon, Lime, Grapefruit)	☐	☐	☐	☐	☐	☐
Stone Fruits…… (eg. Plum, Apricot, Peach, Cherry)	☐	☐	☐	☐	☐	☐
Soft Fruits…… (eg. Raspberry, Strawberry, Redcurrant, Blackberry)	☐	☐	☐	☐	☐	☐
Fleshy Fruits…… (eg. Apple, Pear, Banana, Pineapple)	☐	☐	☐	☐	☐	☐
Vine Fruits…… (eg. Grape, Melon, Cantaloupe)	☐	☐	☐	☐	☐	☐
DAIRY						
Cream……	☐	☐	☐	☐	☐	☐
Butter / Margarine……	☐	☐	☐	☐	☐	☐
Yogurt……	☐	☐	☐	☐	☐	☐
Cheese ……	☐	☐	☐	☐	☐	☐
Egg ……	☐	☐	☐	☐	☐	☐
OTHER FOODS						
Pulses…… (eg. Pea, Bean, Lentil)	☐	☐	☐	☐	☐	☐
Nuts and Seeds……	☐	☐	☐	☐	☐	☐
Soy/Tofu products……. (eg. Soy milk, Tofu, Soya meat)	☐	☐	☐	☐	☐	☐
Sweets and snacks…… (eg. Crisps, cakes, chocolate)	☐	☐	☐	☐	☐	☐

TEA DRINKING

4.2. Which of the following describes your current tea consumption best?

- I drink tea ☐
- I used to drink tea, but I don't anymore ☐
- I have never drunk tea ☐ ***Go to question 4.8***

4.3. At what age did you start drinking tea? ☐☐ *Years old* For as long as I can remember ☐

4.4. At what age did you stop drinking tea? ☐☐ *Years old* Have not stopped ☐

4.5. What strength of tea do/did you usually prefer to drink? (tick appropriate box)

- Weak ☐
- Moderate ☐
- Strong ☐
- Very Strong ☐

4.6. Do/did you add milk to your tea? (tick appropriate box)

- Never ☐
- Rarely ☐
- Sometimes ☐
- Usually ☐
- Always ☐

4.7. Do/did you add sugar to your tea? (tick appropriate box)

- Never ☐
- Rarely ☐
- Sometimes ☐
- Usually ☐
- Always ☐

COFFEE DRINKING

4.8. Which of the following describes your current coffee consumption best?

- I drink coffee ☐
- I used to drink coffee, but I don't anymore ☐
- I have never drunk coffee ☐ ***Go to question 4.14***

4.9. At what age did you start drinking coffee? ☐☐ *Years old* For as long as I can remember ☐

4.10. At what age did you stop drinking coffee? ☐☐ *Years old* Have not stopped ☐

COFFEE DRINKING *(Continued)*

4.11. What strength of coffee do/did you usually prefer to drink? (tick appropriate box)

- Weak ☐
- Moderate ☐
- Strong ☐
- Very Strong ☐

4.12. Do/did you add milk to your coffee? (tick appropriate box)

- Never ☐
- Rarely ☐
- Sometimes ☐
- Usually ☐
- Always ☐

4.13. Do/did you add sugar to your coffee? (tick appropriate box)

- Never ☐
- Rarely ☐
- Sometimes ☐
- Usually ☐
- Always ☐

ALCOHOL DRINKING

4.14. Which of the following describes your alcohol consumption best?

- I drink alcohol ☐
- I used to drink alcohol, but I don't anymore ☐
- I have never drunk alcohol ☐ ***Go to question 4.18***

4.15. How many days a week do/did you usually drink alcohol? ☐

4.16. At what age did you start drinking alcohol? ☐☐ *Years old*

4.17. At what age did you stop drinking alcohol? ☐☐ *Years old* Have not stopped ☐

FLUID INTAKE

4.18. Please indicate how often, during the past year, you have drunk one measure each of the types of drinks that are listed below.

		Average Use Last Year						
	Measure	Never or less than one measure per month	1-3 per month	One a week	2-4 per week	5-6 per week	At least one per day	How many per day?
ALCOHOLIC DRINKS								
Wine or champagne……	1 small glass	☐	☐	☐	☐	☐	☐ →	☐☐
Fortified Wine……. (eg. Port, Sherry, Cinzano)	1 small glass	☐	☐	☐	☐	☐	☐ →	☐☐
Beer……. (eg. Beer, Lager, Stout)	1 Pint	☐	☐	☐	☐	☐	☐ →	☐☐
Cider……	1 Pint	☐	☐	☐	☐	☐	☐ →	☐☐
Spirits…….. (eg. Gin, Brandy, Rum, Vodka, Whisky)	1 pub measure (25cl)	☐	☐	☐	☐	☐	☐ →	☐☐
Liqueurs…….. (eg. Tia Maria, Cointreau, Baileys, Grand Marnier, etc)	1 pub measure (25cl)	☐	☐	☐	☐	☐	☐ →	☐☐
HOT DRINKS								
Coffee……..	1 cup	☐	☐	☐	☐	☐	☐ →	☐☐
Tea……..	1 cup	☐	☐	☐	☐	☐	☐ →	☐☐
Hot Chocolate……	1 cup	☐	☐	☐	☐	☐	☐ →	☐☐
Ovaltine / Horlicks……..	1 cup	☐	☐	☐	☐	☐	☐ →	☐☐
Soup……	1 Cup/ bowl	☐	☐	☐	☐	☐	☐ →	☐☐
SOFT DRINKS								
Fizzy pop…… (eg. Lemonade, Cola)	½ pint glass	☐	☐	☐	☐	☐	☐ →	☐☐
Pure fruit juice……. (eg. Orange, Apple, etc)	½ pint glass	☐	☐	☐	☐	☐	☐ →	☐☐
Fruit squash or cordial……..	½ pint glass	☐	☐	☐	☐	☐	☐ →	☐☐
Milk……..	½ pint glass	☐	☐	☐	☐	☐	☐ →	☐☐
Water ……..	½ pint glass	☐	☐	☐	☐	☐	☐ →	☐☐

SECTION 5: OTHER BEHAVIOURS

ARTIFICIAL SWEETENERS (SUGAR SUBSTITUTES)

5.1. Which of the following describes your artificial sweetener consumption best?

- I use artificial sweeteners ☐
- I used to use artificial sweeteners, but I don't anymore ☐
- I have never used artificial sweeteners ☐ ***Go to question 5.9***

5.2. At what age did you start using artificial sweeteners? ☐☐ *Years old*

5.3. At what age did you stop using artificial sweeteners? ☐☐ *Years old*
☐ Have not stopped

5.4. What is/was the name of your regular brand of sweetener? _____

5.5. What form does/did this sweetener come in?

- Pill or tablet ☐
- Granulated powder ☐
- Liquid ☐

5.6. If this sweetener comes in the form of a pill, on average, how many pills per week do/did you use? ☐☐☐

5.7. If this sweetener comes in the form of granulated powder or liquid, on average, how many teaspoons per week do/did you use? ☐☐☐

5.8. Which of the following brands of sweetener have you ever used?

Sweet'n'Low	☐	Splenda	☐
Natreen	☐	Nutrasweet	☐
Canderel	☐	Sweetex	☐
Sunnet	☐	Flix	☐
Shapers	☐	Natrena	☐
Saxin	☐	Hermesetas	☐
Diamin	☐	Other	☐

'Other' Specify? _____

VITAMINS AND SUPPLEMENTS

5.9. Which of the following describes your use of vitamins and supplements best?

I take vitamins or supplements ☐

I used to take vitamins or supplements, but I don't anymore ☐

I have never taken vitamins or supplements ☐ ***Go to Question 5.11***

5.10. Have you ever taken, any of the following vitamins or supplements for a period of 3 months or more?

Type of Vitamin / Supplement	Yes	no	Unknown	What is the name of your medication?	Where do you buy this product?
Example Example Example Example Example Example					
Multi-vitamins	☐	☑	☐	***ABC Plus Tablets***	***Holland and Barrett***
Multi-vitamins	☐	☐	☐		
Folic Acid	☐	☐	☐		
Vitamin B	☐	☐	☐		
Vitamin C	☐	☐	☐		
Vitamin E	☐	☐	☐		
Iron pills	☐	☐	☐		
Cod liver oil	☐	☐	☐		
Magnesium	☐	☐	☐		
Zinc	☐	☐	☐		
Vitamin B12	☐	☐	☐		
Selenium	☐	☐	☐		
Chromium	☐	☐	☐		
Calcium	☐	☐	☐		
Other (1)	☐	☐	☐		
Other (2)	☐	☐	☐		

If you are taking any vitamins or supplements. Please bring the packet in with you on your next hospital visit

HAIR COLOURING

*Have you **ever** used either permanent or semi permanent hair colouring,*

Yes ☐ ***Please go to question 5.11***

No ☐ ***Please go to question 5.15***

In this section of the questionnaire, we would like you to tell us about your use of semi - permanent or permanent hair colorants to darken, lighten or change the colour of your hair.

This does not include any temporary hair dyes (dyes that last only 6 to 10 washes)

Semi permanent = Hair dyes that last at least a couple of months but eventually wash out.
Permanent = Hair dyes that do not wash out, they grow out with your hair.

5.11. Which of the following best describes your use of **semi permanent** hair colouring?

I currently use semi permanent hair colouring ☐
I have used semi permanent hair colouring in the past, but I don't anymore ☐
I have never used semi permanent hair colouring ☐

5.12. Which of the following best describes your use of **permanent** hair colouring?

I currently use permanent hair colouring ☐
I have used permanent hair colouring in the past, but I don't anymore ☐
I have never used permanent hair colouring ☐

5.13. Please indicate below, which **semi - permanent** colours you have **ever** applied to your hair, how long you kept your hair that colour and how often did you dye it.

Semi - permanent hair colour	Type of application	In total, for how many years did you dye your hair this colour?	Roughly how many times per year do/did you colour your hair?
Blonde	Whole head	☐☐ *years*	☐☐ *times per year*
	Sections of hair (Highlights)	☐☐ *years*	☐☐ *times per year*
Brown	Whole head	☐☐ *years*	☐☐ *times per year*
	Sections of hair (Lowlights)	☐☐ *years*	☐☐ *times per year*
Red / other bright colour	Whole head	☐☐ *years*	☐☐ *times per year*
	Sections of hair	☐☐ *years*	☐☐ *times per year*
Black	Whole head	☐☐ *years*	☐☐ *times per year*

HAIR COLOURING *(Continued)*

5.14. Please indicate below, which **permanent** colours you have **ever** applied to your hair, how long you kept your hair that colour and how often did you dye it.

Permanent hair colour	Type of application	In total, for how many years did you dye your hair this colour?	Roughly how many times per year do/did you colour your hair?
Blonde	Whole head	☐☐ *years*	☐☐ *times per year*
	Sections of hair (Highlights)	☐☐ *years*	☐☐ *times per year*
Brown	Whole head	☐☐ *years*	☐☐ *times per year*
	Sections of hair (Lowlights)	☐☐ *years*	☐☐ *times per year*
Red / other bright colour	Whole head	☐☐ *years*	☐☐ *times per year*
	Sections of hair	☐☐ *years*	☐☐ *times per year*
Black	Whole head	☐☐ *years*	☐☐ *times per year*

INDUSTRIAL CHEMICALS

5.15. Please tell us whether you have ever been exposed to any of the following substances whilst at work and if so for how many years you were exposed.

SUBSTANCE	Yes	No	Unknown	If YES How Many Years were you exposed to this substance
Diesel exhaust fumes	☐	☐	☐	☐☐ *years*
Dyes	☐	☐	☐	☐☐ *years*
Metal Dust	☐	☐	☐	☐☐ *years*
Mineral Oil	☐	☐	☐	☐☐ *years*
Pesticides	☐	☐	☐	☐☐ *years*

SECTION 6: MEDICATIONS

Please indicate which medications you have taken. Where possible, please also record the name of the of the medication that you have taken

6.1. Have you taken any of the following medications regularly for a period of 3 months or more?

Type of Medicine	Yes	No	Unknown	What is the name of your medication?
Example Example Example Example Example Example				
NSAIDS	☑	☐	☐	***Ibuprofen***
Pain killers				
Paracetamol	☐	☐	☐	
Phenacetin	☐	☐	☐	
Aspirin	☐	☐	☐	
NSAID's (eg. Ibuprofen, Brufen, Diclofenac, Volterol)	☐	☐	☐	
Medicine for high cholesterol (eg. Simvastatin, Pravastatin, Atorvastatin)	☐	☐	☐	

6.2. Have you ever taken any of the following medications?

Type of Medicine	Yes	No	Unknown	What is the name of your medication?
Antidepressants, sleeping pills or sedatives	☐	☐	☐	
Chemotherapy	☐	☐	☐	
Immune Suppressants (eg. Steroid Tablets, Cyclosporin)	☐	☐	☐	
Inhaled Steroids	☐	☐	☐	
Women Only: Hormone replacement therapy (HRT)	☐	☐	☐	
Women Only: The contraceptive pill	☐	☐	☐	

SECTION 7: MEDICAL HISTORY

The questions in this section ask about medical conditions you might have had.

Please indicate which conditions you have ever had and which you have never had. For each condition you have had, please give your approximate age (in years) when the condition started.

7.1. Do you have, or have ever had any of the following conditions?

	Yes	No	Not Sure	**IF YES, PLEASE GIVE AGE WHEN IT FIRST STARTED (in years)**
BRAIN and NERVOUS SYSTEM				
Insomnia requiring treatment?.....	☐	☐	☐	☐☐
Depression requiring treatment?.....	☐	☐	☐	☐☐
HEART and CIRCULATORY SYSTEM				
Arrhythmia (Irregular heartbeat or palpitations), requiring medication or follow-up by a doctor?..... **Please describe**.....	☐	☐	☐	☐☐
A myocardial infarction (heart attack)?	☐	☐	☐	☐☐
Pulmonary embolism (obstruction of a blood vessel in the lungs)?.....	☐	☐	☐	☐☐
Hypertension (high blood pressure) requiring medication?.....	☐	☐	☐	☐☐
Hyperlipidaemia (High blood cholesterol)?.....	☐	☐	☐	☐☐
Angina pectoris (chest pains due to lack of oxygen to the heart requiring medication)?.....	☐	☐	☐	☐☐
Migraine?.....	☐	☐	☐	☐☐
Stroke?.....	☐	☐	☐	☐☐
Deep vein thrombosis (Blood clot in head, lung, arm, leg or pelvis)?	☐	☐	☐	☐☐
Ischemic legs (Atherosclerosis / hardening of blood vessels in the legs)?.....	☐	☐	☐	☐☐
CHEST / ALLERGIES				
Bronchitis / emphysema?	☐	☐	☐	☐☐
Hay fever / eczema?.....	☐	☐	☐	☐☐
Asthma?..... **Please describe**.....	☐	☐	☐	☐☐

MEDICAL HISTORY *(Continued)*

	Yes	No	Not Sure	**IF YES, PLEASE GIVE AGE WHEN IT FIRST STARTED (in years)**
DIGESTIVE SYSTEM				
Gallstones? ……	☐	☐	☐	☐☐
Have you had your gall bladder removed?.....	☐	☐	☐	☐☐
Please describe.....				
Liver disease? ……	☐	☐	☐	☐☐
Please describe.....				
Intestinal polyps?.....	☐	☐	☐	☐☐
Bilharzia (parasitic worms) of the bowel?.....	☐	☐	☐	☐☐
BONES				
Arthritis requiring drug treatment for more than 3 months?.....	☐	☐	☐	☐☐
Fracture of the wrist after age 20?.....	☐	☐	☐	☐☐
Fracture of the spine?.....	☐	☐	☐	☐☐
Osteoporosis (brittle bones disease)?.....	☐	☐	☐	☐☐
Fracture of the hip?.....	☐	☐	☐	☐☐
CONGENITAL ABNORMALITIES				
Renal tract abnormalities?.....	☐	☐	☐	☐☐
Please describe.....				
Any other congenital abnormality or birth defect?.....	☐	☐	☐	☐☐
Please describe.....				
OTHER				
Tuberculosis?.....	☐	☐	☐	☐☐
Psychiatric illness other than insomnia or depression?..	☐	☐	☐	☐☐
Please describe.....				
Diabetes controlled by diet?.....	☐	☐	☐	☐☐
Diabetes controlled by insulin injection?.....	☐	☐	☐	☐☐
Diabetes controlled by pills or tablets?……..	☐	☐	☐	☐☐
TUMOURS				
Benign growth (non cancer)?.....	☐	☐	☐	☐☐
Please describe.....				
Cancer, other than your current bladder cancer?.....	☐	☐	☐	☐☐
Please describe.....				
Radiotherapy to lower abdomen or genitals?.....	☐	☐	☐	☐☐
Any kind of chemotherapy?.....	☐	☐	☐	☐☐
Please describe.....				

MEDICAL HISTORY *(Continued)*

	Yes	No	Not Sure	**IF YES, PLEASE GIVE AGE WHEN IT FIRST STARTED (in years)**
URINARY SYSTEM				
Have you ever had kidney stones?.....	☐	☐	☐	☐☐
Have you ever had stones in the bladder?.....	☐	☐	☐	☐☐
Have you had a urinary infection (cystitis) that required antibiotics on more than 1 occasion?.....	☐	☐	☐	☐☐
Have you had any injury requiring a catheter in the bladder for more than 1 month?.....	☐	☐	☐	☐☐
Have you ever had treatment for Bilharzia (schistosomiasis) of the bladder? ……	☐	☐	☐	☐☐
Have you ever had treatment for genital (infective) warts?.....	☐	☐	☐	☐☐
Men Only: Have you had treatment for an enlarged prostate?.....	☐	☐	☐	☐☐
Have you had treatment for an overactive bladder?	☐	☐	☐	☐☐
Were you born with an abnormality that affected your bladder or your control of your bladder? **Please describe**.....	☐	☐	☐	

7.2. Please tell us if there are any chemicals or drugs that you have taken, that you feel may have contributed to your developing bladder cancer?

_____

_____

_____

REPRODUCTIVE HISTORY

Women only:

How many successful pregnancies have you had? ☐☐

How many unsuccessful pregnancies have you had? ☐☐

At what age did you start menstruation? ☐☐ *years old*

At what age did you stop menstruation? ☐☐ *years old* Have not stopped ☐

SECTION 8: SOCIAL SUPPORT (to be completed by the patient)

Here is a list of some things that other people do for us or give us that may be helpful or supportive. Please read each statement carefully and put a tick the box that is closest to your situation.

Example Example Example Example Example Example

	As much as I would like				Much less than I would like
I get enough vacation time……	☐	☑	☐	☐	☐

If you put a check where we have, it means that you get *almost* as much vacation time as you would like, but not quite as much as you would like.

		As much as I would like				Much less than I would like
8.1.	I have people who care what happens to me…….	☐	☐	☐	☐	☐
8.2.	I get love and affection……...	☐	☐	☐	☐	☐
8.3.	I get chance to talk to someone I trust about problems at work or with my housework ……	☐	☐	☐	☐	☐
8.4.	I get chance to talk to someone I trust about my personal and family problems……...	☐	☐	☐	☐	☐
8.5.	I get chance to talk about money matters ……..	☐	☐	☐	☐	☐
8.6.	I get invitations to go out and do things with other people ……..	☐	☐	☐	☐	☐
8.7.	I get useful advice about important things in life ...	☐	☐	☐	☐	☐
8.8.	I get help when I am sick in bed ……..	☐	☐	☐	☐	☐

SECTION 9: GENERAL HEALTH (to be completed by the patient)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the response between 1 and 4 that best applies to you. There are no "right" or "wrong" answers. The answers that you provide will remain strictly confidential.

	Not at all	**A little**	**Quite a bit**	**Very much**
9.1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?.....	1	2	3	4
9.2. Do you have any trouble taking a long walk?.....	1	2	3	4
9.3. Do you have any trouble taking a short walk outside of the house?.....	1	2	3	4
9.4. Do you need to stay in bed or a chair during the day?.....	1	2	3	4
9.5. Do you need help with eating, dressing, washing yourself or using the toilet?.....	1	2	3	4

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
9.6. Were you limited in doing either your work or other daily activities?.....	1	2	3	4
9.7. Were you limited in pursuing your hobbies or other leisure time activities?.....	1	2	3	4
9.8. Were you short of breath?.....	1	2	3	4
9.9. Have you had pain?.....	1	2	3	4
9.10. Did you need to rest?.....	1	2	3	4
9.11. Have you had trouble sleeping?.....	1	2	3	4
9.12. Have you felt weak?.....	1	2	3	4
9.13. Have you lacked appetite?.....	1	2	3	4

GENERAL HEALTH *(Continued)*

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
9.14. Have you felt nauseated?.....	1	2	3	4
9.15. Have you vomited?.....	1	2	3	4
9.16. Have you been constipated?.....	1	2	3	4
9.17. Have you had diarrhea?.....	1	2	3	4
9.18. Were you tired?.....	1	2	3	4
9.19. Did pain interfere with your daily activities?.....	1	2	3	4
9.20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?.....	1	2	3	4
9.21. Did you feel tense?.....	1	2	3	4
9.22. Did you worry?.....	1	2	3	4
9.23. Did you feel irritable?.....	1	2	3	4
9.24. Did you feel depressed?.....	1	2	3	4
9.25. Have you had difficulty remembering things?.....	1	2	3	4
9.26. Has your physical condition or medical treatment interfered with your <u>family</u> life?.....	1	2	3	4
9.27. Has your physical condition or medical treatment interfered with your <u>social</u> life?.....	1	2	3	4
9.28. Has your physical condition or medical treatment caused you financial difficulties?.....	1	2	3	4

For the following questions, please circle the number between 1 and 7 that best applies to you

9.29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

<u>Very Poor</u> …….. <u>Excellent</u>

9.30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

<u>Very Poor</u> …… <u>Excellent</u>

TO BE PRINTED ON HOSPITAL LETTERHEADED PAPER

<Patient Title> <Patient Surname>
<Patient Address 1>
<Patient Address 2>
<Patient Address 3>
<Patient Address 4>
<Patient Address 5>
<Patient Post Code>

<Date>

Dear <Patient Title> <Patient Surname>

RE: Bladder Cancer Prognosis Programme – postal information request

We would like to thank you once again for taking part in the Bladder Cancer Prognosis Programme.

As explained to you by our researcher, we would like you to complete a questionnaire and a diary at home. Completing them at home allows you time to gather the information requested and if necessary to ask other family members or friends for their help to fill it in.

Enclosed in this pack are a **diary** and a **questionnaire**. Each of these documents has full instructions to tell you how to fill them in. Please take time to read the instructions carefully and contact our researcher on the telephone number below if you have any queries.

The diary is to be used to collect information on what you eat and drink during the course of a normal week and also the number of times that you pass water during the course of 3 days. Please start completing the diary as soon as possible after receiving this letter (ideally this will be the next day). It is important that you allow at least 1 week to fill it in before you come back to hospital for your follow-up appointment.

The questionnaire asks about your employment and residential history and your family's history of cancer.

Please bring both the **diary** and the **questionnaire** back to the researcher at the hospital when you are seen at your **next follow-up appointment on <Date of Appointment>**. Your research nurse will go through the questionnaire and diary with you on your return and will be happy to answer any questions.

This information is very important to us and will help us to look into some of the lifestyle factors that can influence the way in which bladder cancers behave.

Thank you again for your continued participation.

Yours sincerely,

<Urologist>

Study Number: ☐☐☐☐

BLADDER CANCER PROGNOSIS PROGRAMME

Cancer Research UK Bladder Cancer Group

Postal Questionnaire

CONFIDENTIAL

VERSION: FINAL 2.0 August 2009

PLEASE DESTROY PREVIOUS VERSIONS

A programme of research

Conducted by: *Funded by:*

UNIVERSITY OF BIRMINGHAM

CANCER RESEARCH UK

INTRODUCTION

As part of the Bladder Cancer Prognosis Programme, we would like to collect information about where you have lived and which types of jobs you have had. We would also like you to tell us about the members of your immediate family and whether or not they have ever had cancer. There are **three** sections in this questionnaire.

- Section 1: Occupational History
- Section 2: Residential History
- Section 3: Family History of Cancer

We would like you to go through each section at a time, reading the instructions at the beginning of each section and looking at the examples that we have provided which, will help you to know how to fill in the questionnaire.

The questions in section 3 ask for personal family information. If you feel that any of the questions are too personal, do not answer them. The questions are not used to test you in any way and the responses that you give will not be used to make any judgements of you. There are no right or wrong answers. All of your responses will be treated as strictly confidential and will be used only for medical research.

You may find that some of the information we are asking you for may not be available (e.g. some postcodes may not exist for some of your past addresses). Do not worry, please remember to provide us with as much detail as possible. Try to answer every question even if the answer is 'I can't remember' or 'I don't know'.

Please post the completed questionnaire to us using the enclosed pre-paid envelope.

If you have any questions or if there is anything that you feel you don't understand, please telephone our researcher at any time on < contact number>.

Thank you again for taking the time to participate in this study.

CANCER RESEARCH UK	**BLADDER CANCER PROGNOSIS PROGRAMME (BCPP)**	POSTAL QUESTIONNAIRE **OCCUPATION HISTORY** Section 1 **Page 1 of 3**

SECTION ONE: OCCUPATIONAL HISTORY

In this section we would like you to tell us about your **most recent job** and all of your **previous jobs** that you have had for one year or more

Here are 3 examples of how to fill in this section of the questionnaire

Most Recent Job # ***Example Example Example Example Example Example***

Time period that you worked there: From year: 1 9 7 2 To year: 1 9 9 6

Job Title:	DRIVER
Description of Activities:	HGV DRIVER
Name of Organisation:	JO BLOGGS BUILDERS
Location (town/city):	BIRMINGHAM
Type of Business:	BUILDING CONTRACTORS

Previous Job # 1 ***Example Example Example Example Example Example***

Time period that you worked there: From year: 1 9 7 2 To year: 1 9 8 6

Job Title:	OFFICE CLERK
Description of Activities:	RECEPTION / OFFICE DUTIES
Name of Organisation:	JO BLOGGS ACCOUNTANTS
Location (town/city):	DUDLEY
Type of Business:	ACCOUNTANCY

Previous Job # 2 ***Example Example Example Example Example Example***

Time period that you worked there: From year: 1 9 6 8 To year: 1 9 7 2

Job Title:	TEACHER
Description of Activities:	TEACHING ENGLISH
Name of Organisation:	JO BLOGGS COMPREHENSIVE SCHOOL
Location (town/city):	CARDIFF
Type of Business:	

Please continue on to the next page:

OCCUPATIONAL HISTORY: *(continued)*

Using **CAPITAL LETTERS** and completing **ONE** section for each job, please list your **most recent job first**, followed by all of your **previous jobs.**

We have allowed enough sections for **up to 5** jobs. If you have had more than 5 jobs, complete all 5 sections of this part of the questionnaire and then continue on a **separate piece of paper**.

Current or Most Recent Job

Time period that you worked there: From year: ____ To year: ____

Job Title:

Description of Activities:

Name of Organisation:

Location (town/city):

Type of Business:

Previous Job # 1

Time period that you worked there: From year: ____ To year: ____

Job Title:

Description of Activities:

Name of Organisation:

Location (town/city):

Type of Business:

Previous Job # 2

Time period that you worked there: From year: ____ To year: ____

Job Title:

Description of Activities:

Name of Organisation:

Location (town/city):

Type of Business:

Please continue on to the next page:

OCCUPATIONAL HISTORY: *(continued)*

Previous Job # 3

Time period that you worked there: From year: ____ To year: ____

Job Title:

Description of Activities:

Name of Organisation:

Location (town/city):

Type of Business:

Previous Job # 4

Time period that you worked there: From year: ____ To year: ____

Job Title:

Description of Activities:

Name of Organisation:

Location (town/city):

Type of Business:

Previous Job # 5

Time period that you worked there: From year: ____ To year: ____

Job Title:

Description of Activities:

Name of Organisation:

Location (town/city):

Type of Business:

Please continue on a separate piece of paper if needed:

SECTION TWO: RESIDENTIAL HISTORY

In this section we would like you to tell us about **your previous addresses**. We only need you to tell us about previous addresses at which you have lived for a period of more than **ONE YEAR** during your life. You do not need to tell us your current address.

Here are **3 examples** of how to fill in this section of the questionnaire

Previous Address # 1: ***Example Example Example Example Example Example***

Time period that you lived there: From year: 1951 To year: 1968

House Number & Street:	220
	HAGLEY ROAD
Location (town/city):	BIRMINGHAM
County:	WEST MIDLANDS
Country:	ENGLAND
Postcode (if known):	B15 IAB

Previous Address # 2: ***Example Example Example Example Example Example***

Time period that you lived there: From year: 1968 To year: 1972

House Number & Street:	350
	NETAJI SUBHAS ROAD
Location (town/city):	CALCUTTA
County:	WEST BENGAL
Country:	INDIA
Postcode (if known):	

Previous Address # 3: ***Example Example Example Example Example Example***

Time period that you lived there: From year: 1972 To year: 1986

House Number & Street:	FLAT 1A, HIGHFIELD TOWER
	7 CHAPEL ASH LANE
Location (town/city):	WOLVERHAMPTON
County:	WEST MIDLANDS
Country:	ENGLAND
Postcode (if known):	WV10 4HT

Please continue on to the next page:

RESIDENTIAL HISTORY: *(continued)*

Using **CAPITAL LETTERS** and completing **ONE** section for each address, please list your all of your **PREVIOUS ADDRESSES** that you have lived at for **more than a year. We do not need you to list your current address.**

We have allowed enough sections for **up to 6** addresses. If you have had more than 6 addresses, complete all 6 sections of this part of the questionnaire and then continue on a **separate piece of paper**.

PREVIOUS ADDRESS # 1

Time period that you lived there: From year: | | | | To year: | | | |

House Number & Street:

Location (town/city):

County:

Country:

Postcode (if known):

PREVIOUS ADDRESS # 2

Time period that you lived there: From year: | | | | To year: | | | |

House Number & Street:

Location (town/city):

County:

Country:

Postcode (if known):

PREVIOUS ADDRESS # 3

Time period that you lived there: From year: | | | | To year: | | | |

House Number & Street:

Location (town/city):

County:

Country:

Postcode (if known):

Please continue onto the next page:

CANCER RESEARCH UK	**BLADDER CANCER PROGNOSIS PROGRAMME (BCPP)**	POSTAL QUESTIONNAIRE **RESIDENTIAL HISTORY** Section 2 **Page 3 of 3**

RESIDENTIAL HISTORY: *(continued)*

PREVIOUS ADDRESS # 4

Time period that you lived there: From year: | | | | To year: | | | |

House Number & Street:

Location (town/city):

County:

Country:

Postcode (if known):

PREVIOUS ADDRESS # 5

Time period that you lived there: From year: | | | | To year: | | | |

House Number & Street:

Location (town/city):

County:

Country:

Postcode (if known):

PREVIOUS ADDRESS # 6

Time period that you lived there: From year: | | | | To year: | | | |

House Number & Street:

Location (town/city):

County:

Country:

Postcode (if known):

Please continue on a separate piece of paper if needed:

SECTION THREE: FAMILY HISTORY OF CANCER

In the following sections we are asking for information on **ALL** members of your **immediate biological family** (i.e. blood relations) and their **medical history** of **cancer.**

You **DO NOT** need to tell us about any **adopted** or **step-relations.** Please tell us whether your **immediate family members** have had **cancer**, which **type of cancer** and their **age** at which the **cancer was diagnosed (**if known).

Here are 6 examples of how to complete this section of the questionnaire:

Example Example Example Example Example Example Example Example

Relation: FATHER

Year of Birth: 1 | 9 | 1 | 1

Have they ever had cancer: Yes ☑ No ☐ Don't know ☐

If Yes, Type of cancer: LUNG

Age at which cancer was diagnosed(if known): 7 | 2 Years old

Example Example Example Example Example Example Example Example

Relation: MOTHER

Year of Birth: 1 | 9 | 1 | 5

Have they ever had cancer: Yes ☐ No ☑ Don't know ☐

If Yes, Type of cancer:

Age at which cancer was diagnosed(if known): | Years old

Example Example Example Example Example Example Example Example

Relation: BROTHER ☑ SISTER ☐

Year of Birth: 1 | 9 | 5 | 1

Have they ever had cancer: Yes ☐ No ☑ Don't know ☐

If Yes, Type of cancer:

Age at which cancer was diagnosed(if known): | Years old

Please continue on to the next page:

SECTION THREE: *(continued)*

Here are some more examples of how to complete Section 3 of the questionnaire:

Example Example Example Example Example Example Example Example

Relation: BROTHER ☐ SISTER ☑

Year of Birth: 1 9 3 9

Have they ever had cancer: Yes ☑ No ☐ Don't know ☐

If Yes, Type of cancer: OVARIAN CANCER

Age at which cancer was diagnosed(if known): 4 5 Years old

Example Example Example Example Example Example Example Example

Relation: SON ☐ DAUGHTER ☑

Year of Birth: 1 9 6 8

Have they ever had cancer: Yes ☐ No ☑ Don't know ☐

If Yes, Type of cancer:

Age at which cancer was diagnosed(if known): Years old

Example Example Example Example Example Example Example Example

Relation: SON ☐ DAUGHTER ☑

Year of Birth: 1 9 7 2

Have they ever had cancer: Yes ☑ No ☐ Don't know ☐

If Yes, Type of cancer: BREAST CANCER

Age at which cancer was diagnosed(if known): Years old

Please continue on to the next page:

SECTION THREE: *(continued)*

In this section we would like you to tell us about your **PARENTS**. Please fill in the table below using **CAPITAL LETTERS** and **completing ONE section** for **EACH parent.**

Relation: **FATHER**

Year of Birth: ☐☐☐☐

Have they ever had cancer: Yes ☐ No ☐ Don't know ☐

If Yes, Type of cancer:

Age at which cancer was diagnosed(if known): ☐☐ Years old

Relation: **MOTHER**

Year of Birth: ☐☐☐☐

Have they ever had cancer: Yes ☐ No ☐ Don't know ☐

If Yes, Type of cancer:

Age at which cancer was diagnosed(if known): ☐☐ Years old

Please continue on to the next page:

SECTION THREE: *(continued)*

In this section we would like you to tell us how many **siblings** you have in your family. We would also like to ask you about your **brothers** and **sisters** medical history of cancer. You **DO NOT** need to tell us about any **adopted** or **step-relations.**

Please fill in the table below using **CAPITAL LETTERS**. Complete **ONE section** for **EACH sibling** by **ticking** the appropriate **box** to **indicate brother** or **sister.**

We have allowed enough sections for **up to 6** siblings. If you have more than 6 siblings, complete all 6 sections of this part of the questionnaire and then continue on a **separate piece of paper**.

HOW MANY SIBLINGS DO YOU HAVE: BROTHERS ☐☐ **SISTERS** ☐☐

Sibling # 1

Relation: Brother ☐ Sister ☐

Year of Birth: ☐☐☐☐

Have they ever had cancer: Yes ☐ No ☐ Don't know ☐

If Yes, Type of cancer:

Age at which cancer was diagnosed(if known): ☐☐ Years old

Sibling # 2

Relation: Brother ☐ Sister ☐

Year of Birth: ☐☐☐☐

Have they ever had cancer: Yes ☐ No ☐ Don't know ☐

If Yes, Type of cancer:

Age at which cancer was diagnosed(if known): ☐☐ Years old

Please continue on to the next page:

SECTION THREE *(continued)*

Sibling # 3

Relation: Brother ☐ Sister ☐

Year of Birth: ☐☐☐☐

Have they ever had cancer: Yes ☐ No ☐ Don't know ☐

If Yes, Type of cancer: _____

Age at which cancer was diagnosed(if known): ☐☐ Years old

Sibling # 4

Relation: Brother ☐ Sister ☐

Year of Birth: ☐☐☐☐

Have they ever had cancer: Yes ☐ No ☐ Don't know ☐

If Yes, Type of cancer: _____

Age at which cancer was diagnosed(if known): ☐☐ Years old

Sibling # 5

Relation: Brother ☐ Sister ☐

Year of Birth: ☐☐☐☐

Have they ever had cancer: Yes ☐ No ☐ Don't know ☐

If Yes, Type of cancer: _____

Age at which cancer was diagnosed(if known): ☐☐ Years old

Sibling # 6

Relation: Brother ☐ Sister ☐

Year of Birth: ☐☐☐☐

Have they ever had cancer: Yes ☐ No ☐ Don't know ☐

If Yes, Type of cancer: _____

Age at which cancer was diagnosed(if known): ☐☐ Years old

Please continue on a separate piece of paper if needed:

SECTION THREE *(continued)*

In this section we would like you to tell us **how** many children you have had. We would also like you to tell us about all of your children's (i.e. blood relations) **medical history of cancer.** You **DO NOT** need to tell us about any **adopted** or **step-relations.**

Please fill in the table below using **CAPITAL LETTERS**. Then complete **ONE** section for EACH child, ticking the appropriate box to indicate son or daughter.

We have allowed enough sections for **up to 6** children. If you have more than 6 children, complete all 6 sections of this part of the questionnaire and then continue on a **separate piece of paper**.

HOW MANY CHILDREN HAVE YOU HAD? SONS ☐☐ **DAUGHTERS** ☐☐

Child # 1

Relation: Son ☐ Daughter ☐

Year of Birth: ☐☐☐☐

Have they ever had cancer: Yes ☐ No ☐ Don't know ☐

If Yes, Type of cancer: ☐

Age at which cancer was diagnosed(if known): ☐☐ Years old

Child # 2

Relation: Son ☐ Daughter ☐

Year of Birth: ☐☐☐☐

Have they ever had cancer: Yes ☐ No ☐ Don't know ☐

If Yes, Type of cancer: ☐

Age at which cancer was diagnosed(if known): ☐☐ Years old

Please continue on to the next page:

SECTION THREE: *(continued)*

Child # 3

Relation: Son ☐ Daughter ☐

Year of Birth: ☐☐☐☐

Have they ever had cancer: Yes ☐ No ☐ Don't know ☐

If Yes, Type of cancer: _____

Age at which cancer was diagnosed(if known): ☐☐ Years old

Child # 4

Relation: Son ☐ Daughter ☐

Year of Birth: ☐☐☐☐

Have they ever had cancer: Yes ☐ No ☐ Don't know ☐

If Yes, Type of cancer: _____

Age at which cancer was diagnosed(if known): ☐☐ Years old

Child # 5

Relation: Son ☐ Daughter ☐

Year of Birth: ☐☐☐☐

Have they ever had cancer: Yes ☐ No ☐ Don't know ☐

If Yes, Type of cancer: _____

Age at which cancer was diagnosed(if known): ☐☐ Years old

Child # 6

Relation: Son ☐ Daughter ☐

Year of Birth: ☐☐☐☐

Have they ever had cancer: Yes ☐ No ☐ Don't know ☐

If Yes, Type of cancer: _____

Age at which cancer was diagnosed(if known): ☐☐ Years old

Please continue on a separate piece of paper if needed

Study Number: ☐☐☐☐

BLADDER CANCER PROGNOSIS PROGRAMME

Cancer Research UK Bladder Cancer Group

7-Day Lifestyle Diary

VERSION: FINAL 1.0 November 2005

PLEASE DESTROY PREVIOUS VERSIONS

A programme of research

Conducted by: UNIVERSITY OF BIRMINGHAM

Funded by: CANCER RESEARCH UK

INTRODUCTION

This Diary is to be used to collect information on what you eat and drink during the course of a normal week and also the number of times that you pass water during the course of 3 days. Please start completing the diary as soon as possible after receiving it (ideally this will be the next day). It is important that you allow at least 1 week to fill it in before you come back to hospital for your follow-up appointment.

The first section of this diary is to be used to record the number of times you visit the toilet to pass water, during the course of 3 days. There is a page to complete for each of the 3 days (pages 2-4) At the top of each page you should write in the date and the day of the week. You should then write the number of times during each hour of the day you have passed water. For example. If you visited the toilet to pass water twice between 9 and 10 am, you would write '2' in the box provided. You don't need to write anything in the boxes next to the hours that you did not visit the toilet.

The second section of this diary is to be used to record what you eat and drink over a period of 7 days. You should start filling this in at the same time as the first section. There are several pages of guidance notes and examples on how to complete the food diary. Please take time to read them carefully and to follow the instructions.

Please bring the completed questionnaire with you to your next hospital follow-up appointment and give it to the research nurse.

If you have any questions or if there is anything that you feel you don't understand, please telephone your research nurse at any time on <research nurse mobile>.

Thank you again for taking the time to participate in this study.

3 Day Micturition Diary

As part of the study we are interested in how often you pass water. We would like you to keep a diary for 3 days recording how frequent you visit the toilet to pass water.

Day No. 1

DATE ☐☐☐☐ 2 0 ☐☐ DAY OF WEEK ☐☐☐☐☐☐☐☐

	Time of Day	Number of times you passed water
	Between 12 midnight –1am……	☐☐ times
	Between 1am –2am……..	☐☐ times
	Between 2am-3am……	☐☐ times
	Between 3am-4am……	☐☐ times
	Between 4am-5am……	☐☐ times
	Between 5am-6am……	☐☐ times
	Between 6am-7am……	☐☐ times
	Between 7am-8am……	☐☐ times
	Between 8am-9am……	☐☐ times
	Between 9am-10am……..	☐☐ times
	Between 10am-11am……	☐☐ times
	Between 11am and 12 Noon……	☐☐ times
	Between 12 Noon –1pm……	☐☐ times
	Between 1pm –2pm……..	☐☐ times
	Between 2pm-3pm……	☐☐ times
	Between 3pm-4pm……	☐☐ times
	Between 4pm-5pm……	☐☐ times
	Between 5pm-6pm……	☐☐ times
	Between 6pm-7pm……	☐☐ times
	Between 7pm-8pm……	☐☐ times
	Between 8pm-9pm……	☐☐ times
	Between 9pm-10pm……..	☐☐ times
	Between 10pm-11pm……	☐☐ times
	Between 11pm and 12 Midnight…….	☐☐ times

Day No. 2

DATE ☐☐☐☐ 2 0 ☐☐ DAY OF WEEK ☐☐☐☐☐☐☐☐

	Time of Day	Number of times you passed water
	Between 12 midnight –1am……	☐☐ times
	Between 1am –2am……..	☐☐ times
	Between 2am-3am……	☐☐ times
	Between 3am-4am……	☐☐ times
	Between 4am-5am……	☐☐ times
	Between 5am-6am……	☐☐ times
	Between 6am-7am……	☐☐ times
	Between 7am-8am……	☐☐ times
	Between 8am-9am……	☐☐ times
	Between 9am-10am……..	☐☐ times
	Between 10am-11am……	☐☐ times
	Between 11am and 12 Noon……	☐☐ times
	Between 12 Noon –1pm……	☐☐ times
	Between 1pm –2pm……..	☐☐ times
	Between 2pm-3pm……	☐☐ times
	Between 3pm-4pm……	☐☐ times
	Between 4pm-5pm……	☐☐ times
	Between 5pm-6pm……	☐☐ times
	Between 6pm-7pm……	☐☐ times
	Between 7pm-8pm……	☐☐ times
	Between 8pm-9pm……	☐☐ times
	Between 9pm-10pm……..	☐☐ times
	Between 10pm-11pm……	☐☐ times
	Between 11pm and 12 Midnight…….	☐☐ times

Day No. 3

DATE ☐☐ ☐☐ 20☐☐ DAY OF WEEK

	Time of Day	Number of times you passed water
	Between 12 midnight –1am……	☐☐ *times*
	Between 1am –2am……..	☐☐ *times*
	Between 2am-3am……	☐☐ *times*
	Between 3am-4am……	☐☐ *times*
	Between 4am-5am……	☐☐ *times*
	Between 5am-6am……	☐☐ *times*
	Between 6am-7am……	☐☐ *times*
	Between 7am-8am……	☐☐ *times*
	Between 8am-9am……	☐☐ *times*
	Between 9am-10am……..	☐☐ *times*
	Between 10am-11am……	☐☐ *times*
	Between 11am and 12 Noon……	☐☐ *times*
	Between 12 Noon –1pm……	☐☐ *times*
	Between 1pm –2pm……..	☐☐ *times*
	Between 2pm-3pm……	☐☐ *times*
	Between 3pm-4pm……	☐☐ *times*
	Between 4pm-5pm……	☐☐ *times*
	Between 5pm-6pm……	☐☐ *times*
	Between 6pm-7pm……	☐☐ *times*
	Between 7pm-8pm……	☐☐ *times*
	Between 8pm-9pm……	☐☐ *times*
	Between 9pm-10pm……..	☐☐ *times*
	Between 10pm-11pm……	☐☐ *times*
	Between 11pm and 12 Midnight…….	☐☐ *times*

FOOD DIARY

We would like you to keep this diary of everything you eat and drink over the next seven days.

It is very important that you do not adjust what you eat and drink just because you are keeping a record. Please continue to eat whatever you wish.

Instructions

As you will see, each day is marked in sections, beginning with the first thing in the morning and ending with bedtime. For each part of the day write down all food and drink consumed, the amounts, and description if necessary. If nothing is eaten or drunk during a part of the day, draw a line through that section. Record everything at the time of eating, not from memory at the end of the day.

On the next eight pages is a list of popular foods and drinks. Next to each item is the sort of thing we need to know so that we can tell what it is made of and how much you had. This list cannot cover all the foods and drinks, so try to relate to a similar item if any that you have eaten are missing. Please give as much detail as you can. There is an example on page 17.

For some foods you may find it easier to describe how much you had by comparing it to one of the photographs on pages 13 to 17.

Many packet foods have weights printed on them, so please use these to show how much you ate.

At the end of each day there is a list of snacks and drinks that can easily be forgotten. Please write any extra items in here if you have not already recorded them in some other part of the day.

FOR EACH ITEM THAT YOU EAT OR DRINK PLEASE READ THE FOLLOWING FOR DETAILS REQUIRED:

Always state what sort of **oil** or **fat** was used for baking, frying etc.

Give **brand and full name** of products where possible.

For **meals/snacks eaten away from home**, please note where these items were eaten, giving name and/or type of restaurant, café, pub etc., where appropriate.

Please could you answer the questions at the back (pages 53-56) **after** you have completed the seven days of the diary.

Please remember to provide us with as much detail as you possibly can.

WHERE POSSIBLE, ALWAYS STATE WHAT SORT OF OIL OR FAT WAS USED FOR BAKING, FRYING ETC.		
Food/Drink	**Description & Preparation**	**Amount**
Home-made dishes	Please say what the dish is called and give recipe or ingredients, including amounts, if possible	tablespoons, or one of the pictures
Ready-made meals	What sort: e.g. pizzas, microwave dishes, slimmers' meals etc. Please give main ingredients and nutrition information on packet, and enclose label or bar code if possible.	Weight from packet
Meals eaten away from home	What sort: e.g. pizzas, Chinese, Indian dishes, fish and chips, hamburgers, hot dogs etc. Please say what the dish is called and give ingredients where possible. Give name of the restaurant if it is a well known chain.	Tablespoons, number or one of the pictures

WHERE POSSIBLE, ALWAYS STATE WHAT SORT OF OIL OR FAT WAS USED FOR BAKING, FRYING ETC.		
Food/Drink	**Description & Preparation**	**Amount**
Bacon	Lean or streaky; fried or grilled rashers	Number
Baked beans	Standard or reduced sugar/salt	Tablespoons, tin size or picture 12
Beefburger (hamburger)	Home-made, from a packet or take away; fried, microwaved or grilled; well done, rare etc; large or small; with or without bread roll	Number
Beer	Stout, bitter, lager, keg, draught, bottled, canned, low alcohol, strong, home-made; give brand if possible; % alcohol	Number of pints/half pints, cans/bottles, including size
Biscuits	Plain; savoury; cheese, crispbread, sweet, chocolate, wafer, home-made; size; include biscuits like Kit-Kat and Penguin; write in the name and brand if you can	Number
Bread (see also sandwiches)	Wholemeal, white or brown; currant, fruit, malt; large or small loaf; thick, medium or thin slices; sliced or unsliced; give brand if possible	Number of slices
Bread rolls	Wholemeal, white or brown; alone or with filling (see sandwiches); size; crusty or soft; give brand if possible	Number of rolls
Breakfast cereal, bran, wheatgerm	What sort; cornflakes, Weetabix, muesli etc.; give brand if possible	Number of biscuits, tablespoons or picture 1
Bun	What sort; iced currant; sweet or plain; large or small; give name and brand if possible	Number
Butter for bread	Ordinary or low fat dairy spread, write in the name and brand if you can	Thick, average, thin spread

WHERE POSSIBLE, ALWAYS STATE WHAT SORT OF OIL OR FAT WAS USED FOR BAKING, FRYING ETC.		
Food/Drink	**Description & Preparation**	**Amount**
Cake-small	What sort; cream, iced; sort of filling; give name and brand if possible	Number
Cake-large	What sort; cream, iced; sort of filling; give name and brand if possible	Slices or pictures 15 or 16
Cheese	What sort; cream, cottage, hard, soft; low fat; write in the name if you can	Tablespoons or picture 2
Chips	Fresh, frozen, oven, microwave or crinkle cut; type of fat for cooking; give brand if possible	Picture 7
Chocolate	What sort; plain, milk, white, diabetic; give name and brand if possible	Number or bar weight
Chops	What sort; lean or fatty; large or small; fried, grilled, baked etc; well done, rare etc.	Number
Cider	Sweet, dry, vintage, low alcohol; % alcohol	Pints and half pints; number of cans/bottles; including size
Coffee	With/without milk, what sort, half milk/half water; all milk, ground, instant, decaffeinated/caffeinated; strong, average or weak	Cups or mugs
Condiments	Pepper, salt or substitute	½ or ¼ teaspoon, pinch etc.
Cooking oil	Type; brand name	Teaspoons
Cream	Half, single, sour, whipping, double, clotted; low fat; fresh or substitute; sweetened or unsweetened	Tablespoons
Crisps	Brand name; low fat; low salt	Packet weight
Egg	How was it cooked; boiled, fried, scrambled, poached, omelette, etc.	Number

WHERE POSSIBLE, ALWAYS STATE WHAT SORT OF OIL OR FAT WAS USED FOR BAKING, FRYING ETC.		
Food/Drink	**Description & Preparation**	**Amount**
Fish	What sort; fried, boiled, grilled, poached, microwaved; pickled, smoked or salted; with batter or breadcrumbs; tinned with oil or tomato sauce; size; give brand name where applicable	Helping, number or picture 6
Fish cakes or finger	What sort; large, medium or small size; fried or grilled; give brand name if possible	Number
Fruit-fresh	What sort and variety e.g. Cox apple; cored; with or without skin	Number
Fruit-stewed or canned	What sort and variety e.g. Bramley apple; with or without sugar; in fruit juice or syrup	Tablespoons or in tin size
Fruit-juice	What sort; sweetened or unsweetened	Glasses or cups
Gravy	Thick or thin, instant or packet, made with or without dripping, meat juices etc.	Tablespoons
Herbs	Type, fresh or dried	½ or ¼ teaspoons
Honey, jam	Type, specify if low sugar	Teaspoons
Ice-cream	Dairy or non-dairy; flavour or variety	tablespoons
Liver, kidney	Pig, lamb, ox; fried or stewed	Picture 4 or 5
Margarine	Hard, soft, polyunsaturated, low fat, very low fat; give name and brand if possible	Thick, average or thin spread
Marmalade	Type and brand; specify if low sugar	Teaspoons; thick, average or thin spread
Mayonnaise	Give name and brand; state if low fat	Teaspoons
Meat pie, pastie, pastry	What sort; individual or helping; size; fat used for pastry; give brand name where possible	Number or picture 3

WHERE POSSIBLE, ALWAYS STATE WHAT SORT OF OIL OR FAT WAS USED FOR BAKING, FRYING ETC.		
Food/Drink	**Description & Preparation**	**Amount**
Meats	What sort; lean or fatty; fried, microwaved, grilled, roast, barbecued; well done or rare etc; with or without gravy, cut used; pickled, smoked or salted	Slices, helping or pictures 4 or 5
Milk-for drinking on its own or for cereals	Full cream, silver top, semi-skimmed, skimmed, sterilized, UHT, flavoured, powdered, soya	Pints, glasses or cups
Minced beef	On its own, with vegetables, fatty or lean	Tablespoons or picture 5
Peanuts	Dry roasted or ordinary salted	Packet weight
Porridge	With sugar or honey; with milk, cream or water	Bowls
Potatoes	Baked, boiled; with or without skin; mashed, creamed, fried/chips, instant, roast; with butter, margarine etc.	Tablespoons, or pictures 10 or 11
Pudding	What sort and brand; e.g. steamed sponge; with fruit; pie (what sort); jelly; blancmange; mousse; instant desserts; milk puddings, give recipe	Tablespoons, slices or pictures 3, 15 or 17
Rice	Brown or white; boiled or fried; rice pudding	Tablespoons or picture 8
Salad	Describe ingredients, with dressing; what sort of dressing (e.g. oil and vinegar, salad cream, mayonnaise)	Tablespoons or picture 14
Sandwiches and rolls	Wholemeal, white or brown bread; type of filling; butter or margarine; large or small loaf; thick, medium or thin slices	Number of rolls or slices of bread
Sauce-cold	What sort; e.g. tomato ketchup, brown sauce, soy sauce; salad cream; sweet or savoury	Tablespoons or picture 12

WHERE POSSIBLE, ALWAYS STATE WHAT SORT OF OIL OR FAT WAS USED FOR BAKING, FRYING ETC.		
Food/Drink	**Description & Preparation**	**Amount**
Sauce-hot	(for vegetables, meat or fish; puddings) what sort; savoury or sweet; thick or thin, give recipe if possible	Tablespoons or picture 12
Sausages	What sort; e.g. pork, beef, pork and beef; low fat; large or small; how cooked	Number
Sausage rolls	Large or small, type of pastry	Number
Scones	What sort; with currants, sweet or plain; cheese	Number
Snacks-in packet	What sort; e.g. cheese straws, Twiglets, pretzels (give brand name)	Packet weight or number
Soft drinks	Squash, undiluted or diluted; fizzy drinks; low calorie; give brand name	Glasses or cans
Soup	What sort; canned, packet, instant or vending machine, home-made; give brand name	Tablespoons; bowl or mug
Soya, Quorn	TVP, mince, burgers or tofu	Number or pictures 4 or 5
Spaghetti, other pasta	Canned, boiled; white, wholemeal; in sauce; give name and brand where applicable	Tablespoons or picture 9
Spices	Type	½ or ¼ teaspoons
Spreads	On bread, what sort of bread	½ or ¼ teaspoons; thick, average or thin spread
Spirits	What sort; e.g. whisky, gin, vodka, rum; at home or in pub	Single measures as in pub
Sugar	Added to cereals, tea, coffee, fruit etc; what sort; e.g. white, brown, Demerara	Heaped or level teaspoons

WHERE POSSIBLE, ALWAYS STATE WHAT SORT OF OIL OR FAT WAS USED FOR BAKING, FRYING ETC.		
Food/Drink	**Description & Preparation**	**Amount**
Sweets	What sort; e.g. toffees or boiled sweets; diabetic; give name and brand if possible	Number or packet size
Tea	With or without milk; what sort; herb, fruit, decaffeinated/caffeinated; tea bag or leaves; strong, average or weak	Cups or mugs
Vegetables	What sort and variety; with butter, other fat or sauce; fresh, frozen or canned; how cooked e.g. fried, boiled, microwaved or raw	Tablespoons or pictures 12, 13 or 14
Water	State whether tap, filtered, or bottled; give name and brand where applicable	Glasses or bottle size
Wine, sherry, port	White, red; sweet, medium, dry; low alcohol	Glasses or bottle size
Yoghurt, fromage frais	What sort; e.g. with fruit, natural, plain; flavour; low fat, Greek, creamy, soya; give full name and brand if possible	Carton weight/size or tablespoons

Use the pictures to help you to indicate the size of the portion you have eaten. Write down the picture number and size nearest to you own helping e.g. 2a, 3b, 1c etc.

The pictures could also be used for foods not shown e.g. fruit crumble might be a similar portion to shepherd's pie, fruit cake similar to veal and ham pie, and baked beans similar to peas.

Remember that the picture sizes are much smaller than life size. The arrow across the middle of the page indicates a dinner plate 10 inches in width.

1a

1b

1c

2a

2b

2c

3a

3b

3c

4a

4b

4c

8a

8b

8c

5a

5b

5c

9a

9b

9c

10"

Plate

6a

6b

6c

10a

10b

10c

7a

7b

7c

11a

11b

11c

12a

12b

12c

16a

16b

16c

13a

13b

13c

17a

17b

17c

10"

Plate

14a

14b

14c

15a

15b

15c

LUNCH		
Food/Drink	Description and Preparation	Amount
Soup	*Campbell's condensed cream of mushroom, diluted half and half with water*	*1 medium bowl*
Bread	*White, large loaf Sunblest*	*2 medium slices*
Butter	*Anchor salted*	*Thick spread on each slice*
Biscuits	*Jacob's Cream Crackers*	*4*
Cheese	*Tesco matured cheddar*	*2a*
Tomatoes	*Fresh*	*2 medium*
Cake	*Home-made Victoria sponge with jam filling (see recipe)*	*15b*
Tea	Tetley's tea bag, weak	*2 cups*
Milk	Silver top, full cream	*1 tablespoon in each cup*
Sugar	*White granulated*	*2 heaped teaspoons in each*

Day No. 1

DATE ☐☐ ☐☐ 20☐☐ DAY OF WEEK

BEFORE BREAKFAST

Food/Drink	Description and Preparation	Amount

BREAKFAST

Food/Drink	Description and Preparation	Amount

MID MORNING- between breakfast time and lunch time

Food/Drink	Description and Preparation	Amount

LUNCH

Food/Drink	Description and Preparation	Amount

TEA		
Food/Drink	Description and Preparation	Amount
EVENING MEAL		
Food/Drink	Description and Preparation	Amount

LATER EVENING- up to last thing at night		
Food/Drink	Description and Preparation	Amount

BETWEEN MEALS, SNACKS AND DRINKS if not already written in before		
Food/Drink	Description and Preparation	Amount
Chocolate		
Toffees, sweets		
Crisps, peanuts		
Other snacks		
Beer, wine		
Sherry, Spirits		
Other cold drinks		
Tea, coffee		
Other hot drinks		
Ice cream		
Anything else?		

Space to write in the recipe or ingredients of any home-made dishes, take-away meals etc. that you have mentioned but not described previously. Where applicable, please list amounts of ingredients and brand names. For recipes, take-away meals etc., **please indicate amount/proportion actually consumed by yourself.**
END OF DAY No. 1

Day No. 2		
DATE ☐☐ ☐☐ 20☐☐ **DAY OF WEEK**		
BEFORE BREAKFAST		
Food/Drink	Description and Preparation	Amount
BREAKFAST		
Food/Drink	Description and Preparation	Amount

MID MORNING- between breakfast time and lunch time		
Food/Drink	Description and Preparation	Amount
LUNCH		
Food/Drink	Description and Preparation	Amount

TEA		
Food/Drink	Description and Preparation	Amount
EVENING MEAL		
Food/Drink	Description and Preparation	Amount

LATE EVENING- up to last thing at night		
Food/Drink	Description and Preparation	Amount

BETWEEN MEALS, SNACKS AND DRINKS if not already written in before		
Food/Drink	Description and Preparation	Amount
Chocolate		
Toffees, sweets		
Crisps, peanuts		
Other snacks		
Beer, wine		
Sherry, Spirits		
Other cold drinks		
Tea, coffee		
Other hot drinks		
Ice cream		
Anything else?		

Space to write in the recipe or ingredients of any home-made dishes, take-away meals etc. that you have mentioned but not described previously. Where applicable, please list amounts of ingredients and brand names. For recipes, take-away meals etc., **please indicate amount/proportion actually consumed by yourself.**
END OF DAY No. 2

Day No. 3

DATE ☐☐ ☐☐ 20☐☐ DAY OF WEEK

BEFORE BREAKFAST

Food/Drink	Description and Preparation	Amount

BREAKFAST

Food/Drink	Description and Preparation	Amount

MID MORNING- between breakfast time and lunch time

Food/Drink	Description and Preparation	Amount

LUNCH

Food/Drink	Description and Preparation	Amount

TEA		
Food/Drink	Description and Preparation	Amount
EVENING MEAL		
Food/Drink	Description and Preparation	Amount

LATER EVENING- up to last thing at night		
Food/Drink	Description and Preparation	Amount

BETWEEN MEALS, SNACKS AND DRINKS if not already written in before		
Food/Drink	Description and Preparation	Amount
Chocolate		
Toffees, sweets		
Crisps, peanuts		
Other snacks		
Beer, wine		
Sherry, Spirits		
Other cold drinks		
Tea, coffee		
Other hot drinks		
Ice cream		
Anything else?		

Space to write in the recipe or ingredients of any home-made dishes, take-away meals etc. that you have mentioned but not described previously. Where applicable, please list amounts of ingredients and brand names. For recipes, take-away meals etc., **please indicate amount/proportion actually consumed by yourself.**

END OF DAY No. 3

Day No. 4

DATE ☐☐ ☐☐ 20☐☐ **DAY OF WEEK**

BEFORE BREAKFAST

Food/Drink	Description and Preparation	Amount

BREAKFAST

Food/Drink	Description and Preparation	Amount

MID MORNING- between breakfast time and lunch time		
Food/Drink	Description and Preparation	Amount
LUNCH		
Food/Drink	Description and Preparation	Amount

TEA		
Food/Drink	Description and Preparation	Amount
EVENING MEAL		
Food/Drink	Description and Preparation	Amount

LATER EVENING- up to last thing at night		
Food/Drink	Description and Preparation	Amount

BETWEEN MEALS, SNACKS AND DRINKS if not already written in before		
Food/Drink	Description and Preparation	Amount
Chocolate		
Toffees, sweets		
Crisps, peanuts		
Other snacks		
Beer, wine		
Sherry, Spirits		
Other cold drinks		
Tea, coffee		
Other hot drinks		
Ice cream		
Anything else?		

Space to write in the recipe or ingredients of any home-made dishes, take-away meals etc. that you have mentioned but not described previously. Where applicable, please list amounts of ingredients and brand names. For recipes, take-away meals etc., **please indicate amount/proportion actually consumed by yourself.**

END OF DAY No. 4

Day No. 5

DATE ☐☐ ☐☐ 20☐☐ DAY OF WEEK

BEFORE BREAKFAST

Food/Drink	Description and Preparation	Amount

BREAKFAST

Food/Drink	Description and Preparation	Amount

MID MORNING- between breakfast time and lunch time

Food/Drink	Description and Preparation	Amount

LUNCH

Food/Drink	Description and Preparation	Amount

TEA		
Food/Drink	Description and Preparation	Amount
EVENING MEAL		
Food/Drink	Description and Preparation	Amount

LATER EVENING- up to last thing at night		
Food/Drink	Description and Preparation	Amount

BETWEEN MEALS, SNACKS AND DRINKS if not already written in before		
Food/Drink	Description and Preparation	Amount
Chocolate		
Toffees, sweets		
Crisps, peanuts		
Other snacks		
Beer, wine		
Sherry, Spirits		
Other cold drinks		
Tea, coffee		
Other hot drinks		
Ice cream		
Anything else?		

Space to write in the recipe or ingredients of any home-made dishes, take-away meals etc. that you have mentioned but not described previously. Where applicable, please list amounts of ingredients and brand names. For recipes, take-away meals etc., **please indicate amount/proportion actually consumed by yourself.**
END OF DAY No. 5

Day No. 6		
DATE ☐☐ ☐☐ 20☐☐ **DAY OF WEEK**		
BEFORE BREAKFAST		
Food/Drink	Description and Preparation	Amount
BREAKFAST		
Food/Drink	Description and Preparation	Amount

MID MORNING- between breakfast time and lunch time		
Food/Drink	Description and Preparation	Amount
LUNCH		
Food/Drink	Description and Preparation	Amount

TEA		
Food/Drink	Description and Preparation	Amount
EVENING MEAL		
Food/Drink	Description and Preparation	Amount

LATER EVENING- up to last thing at night		
Food/Drink	Description and Preparation	Amount

BETWEEN MEALS, SNACKS AND DRINKS if not already written in before		
Food/Drink	Description and Preparation	Amount
Chocolate		
Toffees, sweets		
Crisps, peanuts		
Other snacks		
Beer, wine		
Sherry, Spirits		
Other cold drinks		
Tea, coffee		
Other hot drinks		
Ice cream		
Anything else?		

Space to write in the recipe or ingredients of any home-made dishes, take-away meals etc. that you have mentioned but not described previously. Where applicable, please list amounts of ingredients and brand names. For recipes, take-away meals etc., **please indicate amount/proportion actually consumed by yourself.**

END OF DAY No. 6

Day No. 7

DATE ☐☐ ☐☐ 20☐☐ DAY OF WEEK

BEFORE BREAKFAST

Food/Drink	Description and Preparation	Amount

BREAKFAST

Food/Drink	Description and Preparation	Amount

MID MORNING- between breakfast time and lunch time

Food/Drink	Description and Preparation	Amount

LUNCH

Food/Drink	Description and Preparation	Amount

TEA		
Food/Drink	Description and Preparation	Amount
EVENING MEAL		
Food/Drink	Description and Preparation	Amount

LATER EVENING- up to last thing at night		
Food/Drink	Description and Preparation	Amount

BETWEEN MEALS, SNACKS AND DRINKS if not already written in before		
Food/Drink	Description and Preparation	Amount
Chocolate		
Toffees, sweets		
Crisps, peanuts		
Other snacks		
Beer, wine		
Sherry, Spirits		
Other cold drinks		
Tea, coffee		
Other hot drinks		
Ice cream		
Anything else?		

Space to write in the recipe or ingredients of any home-made dishes, take-away meals etc. that you have mentioned but not described previously. Where applicable, please list amounts of ingredients and brand names. For recipes, take-away meals etc., **please indicate amount/proportion actually consumed by yourself.**

END OF DAY No. 7

GENERAL QUESTIONS ABOUT YOUR FOOD/DRINK LAST WEEK

1. Which type of milk did you most often use last week? **Select one only**

Full Cream, silver ☐ Semi-skimmed, red/white ☐
Skimmed, fat free ☐ Channel Islands, gold ☐
Sterilized ☐ Dried milk ☐
Soya ☐ State type _____ Homogenized ☐
None ☐
Other ☐ State type _____

2. How much milk do you usually have in tea?

A lot ☐ Average ☐ Hardly any ☐
None ☐ I did not drink tea ☐ Hardly any ☐

3. How much milk do you usually have in coffee?

A lot ☐ Average ☐ Hardly any ☐
None ☐ I did not drink coffee ☐ Hardly any ☐

4. Did you drink decaffeinated tea?

Always ☐ Sometimes ☐ Never ☐

5. Did you drink decaffeinated coffee?

Always ☐ Sometimes ☐ Never ☐

6. Which types of fat did you use last week for baking, frying and spreading ?

What did you use it for?

	Brand name & type used	Baking	Frying	Spreading	Salads
Butter		☐	☐	☐	☐
Low fat spread		☐	☐	☐	☐
Very low fat spread		☐	☐	☐	☐
Polyunsaturated margarine		☐	☐	☐	☐
Other soft margarine		☐	☐	☐	☐
Hard margarine		☐	☐	☐	☐
Vegetable oils		☐	☐	☐	☐
White vegetable fat		☐	☐	☐	☐
Lard		☐	☐	☐	☐
Dripping		☐	☐	☐	☐
Other		☐	☐	☐	☐

7. Which type of bread did you eat most often last week? Select one only

White ☐ Soft grain ☐ Granary ☐

Brown, wheatgerm, Hovis ☐ Wholemeal ☐

Other ☐ *Name of 'Other'* ☐

8. If you ate butter, margarine or spread last week, please tick boxes below to show whether you ate it on toast, bread or in sandwiches:

	Always	Sometimes	Never	Don't Know
Toast	☐	☐	☐	☐
Bread	☐	☐	☐	☐
Sandwiches	☐	☐	☐	☐

9. How thickly did you eat spread, butter, margarine etc. on bread or biscuits?

Thick ☐ Medium ☐ Thin ☐ None ☐

10. If you ate grilled, fried, barbequed or roast meat last week, how well cooked was it?

Beef, lamb, pork		**Poultry**	
Well done/dark brown	☐	Well done/dark brown	☐
Medium	☐	Medium	☐
Lightly cooked/rare	☐	Lightly cooked/rare	☐
Did not eat beef, lamb, pork cooked by these methods	☐	Did not eat poultry cooked by these methods	☐

11. If you ate meat last week, what did you do with the visible fat?

Ate all of the fat ☐ Ate most of the fat ☐

Ate some of the fat ☐ Ate as little as possible ☐

Did not eat meat ☐

12. If you ate poultry last week, did you eat the skin?

Yes ☐ No ☐ Sometimes ☐

Don't know ☐ Did not eat poultry ☐

13. If you had gravy last week, were the meat juices, pan residues or dripping put into the gravy?

Yes ☐ No ☐ Sometimes ☐

Don't know ☐ Didn't have gravy ☐

14. Was salt usually added to your food during cooking last week?

Yes ☐ No ☐ Don't know ☐

Did you usually add salt to your food at the table last week?

Yes ☐ No ☐ Don't know ☐

Did you regularly use a salt substitute (e.g. LoSalt) last week?

Yes ☐ No ☐ Don't know ☐

If YES, which brand ☐

15. Did you eat the skin on fruit? Please tick boxes.

	Skin eaten	**Skin not eaten**	**Fruit not eaten**
Apple	☐	☐	☐
Pear	☐	☐	☐

16. Please name any vitamins, minerals or other food supplements taken on each day of last week. Please write down all the details from each packet/container, and enclose label(s) giving ingredients and individual amounts where possible.

Brand	Name (please list full name)	Amount taken per day-number of pills, capsules or teaspoons	Tick box (es) to show which day(s) supplement was taken last week						
			M	T	W	T	F	S	S
Healthcrafts	*Multivitamins with iron and calcium*	*1 tablet*	✓	✓	✓		✓	✓	✓

EXAMPLE

17. Please complete the table below to show which types of water you consumed last week. Tick which type was used most often for both HOT and COLD drinks.

Water Type	Hot drinks	Cold drinks
Tap water		
Filtered water-hard water filter		
Filtered water-other		
Bottled water-please write down brand		
Other water-please write down name		

18. Were any of the following foods which you ate last week produced organically (without pesticides)? Please tick the necessary box(es).

Vegetables, homegrown	☐	Vegetables, purchased	☐
Fruit, homegrown	☐	Fruit, purchased	☐
Milk and dairy products	☐	Cereals, bread or cereal products	☐
Meat	☐	No organic foods eaten	☐

This space has been left for you to tell us about anything else which you feel is important about your food/drink intake last week.

……
……
……
……
……
……
……
……
……

Study Number: ☐☐☐☐

BLADDER CANCER PROGNOSIS PROGRAMME

Cancer Research UK Bladder Cancer Group

Follow-up Questionnaire

CONFIDENTIAL

VERSION: FINAL 1.0 November 2005

PLEASE DESTROY PREVIOUS VERSIONS

A programme of research

Conducted by: *Funded by:*

UNIVERSITY OF BIRMINGHAM

CANCER RESEARCH UK

CANCER RESEARCH UK	**BLADDER CANCER PROGNOSIS PROGRAMME (BCPP)**	FOLLOW-UP QUESTIONNAIRE **INTRODUCTION & INTERVIEW DETAILS**

Patient Identifier: *First 3 letters from the surname followed by first 2 letters from the forename*			☐☐☐☐☐ *eg: John Smith = SMIJO*
Date of Interview: Time Interview Started *(24hour)*	D D M M Y Y Y Y ☐☐ : ☐☐	Name of Interviewer: Hospital Name:	_____ _____
Will the interview take place with the support of a translator			Yes ☐ No ☐

INTRODUCTION

Some time ago we asked you to tell us some information about yourself and your lifestyle as part of the research study called the Bladder Cancer Prognosis Programme. In order for us to have really good information for our study, we need to know if any of the things we asked you about before have changed since you completed the last questionnaire.

We would therefore like to take you through some questions that ask about any changes that have occurred since last time, so that we can add this new information to the existing information. The questionnaire is much shorter than the first one and will take approximately half an hour.

The questions that you will be asked will include questions about your lifestyle, your behaviours, your health and the help and support you receive from the people around you.

There may be some questions that you think are unusual. The questions are not used to test you in any way and the responses that you give will not be used to make any judgements of you. There are no right or wrong answers. All of your responses will be treated as strictly confidential and will be used only for medical research.

Some of the questions ask for personal information. If you feel that any of the questions are too personal, do not answer them. However, by answering these questions, you will help us to discover links between lifestyles and health.

I <researcher> will take you through each question and keep a record of your responses. There is no time limit, so if you want a little time to think about any of the questions please do so. Try to answer every question even if the answer is 'I can't remember' or 'I don't know'.

If you have any other questions or if there is anything that you feel you don't understand, please ask me <researcher> at any time.

Thank you again for taking the time to participate in this study

SECTION 1: SMOKING BEHAVIOUR

1.1. Have you smoked at all since *<month and year of last questionnaire>*

Yes ☐ ***Go to question 1.2***

No ☐ ***Go to question 2.1***

1.2. Please tell us during which months since *<month and year of last questionnaire>* you have smoked each of the following types of tobacco and how frequently.
(Only fill in the months between last questionnaire and current questionnaire)

	FILTER CIGARETTES			NON-FILTER / HAND-ROLLED CIGARETTES		
	Have you smoked Filter Cigarettes at all during the following months?		If ***Yes***, How many per week?	Have you smoked Non-Filter or hand rolled Cigarettes at all during the following months?		If ***Yes***, How many per week?
	YES	**NO**		**YES**	**NO**	
January	☐	☐	☐☐	☐	☐	☐☐
February	☐	☐	☐☐	☐	☐	☐☐
March	☐	☐	☐☐	☐	☐	☐☐
April	☐	☐	☐☐	☐	☐	☐☐
May	☐	☐	☐☐	☐	☐	☐☐
June	☐	☐	☐☐	☐	☐	☐☐
July	☐	☐	☐☐	☐	☐	☐☐
August	☐	☐	☐☐	☐	☐	☐☐
September	☐	☐	☐☐	☐	☐	☐☐
October	☐	☐	☐☐	☐	☐	☐☐
November	☐	☐	☐☐	☐	☐	☐☐
December	☐	☐	☐☐	☐	☐	☐☐
January	☐	☐	☐☐	☐	☐	☐☐
February	☐	☐	☐☐	☐	☐	☐☐
March	☐	☐	☐☐	☐	☐	☐☐
April	☐	☐	☐☐	☐	☐	☐☐
May	☐	☐	☐☐	☐	☐	☐☐
June	☐	☐	☐☐	☐	☐	☐☐
July	☐	☐	☐☐	☐	☐	☐☐
August	☐	☐	☐☐	☐	☐	☐☐
September	☐	☐	☐☐	☐	☐	☐☐
October	☐	☐	☐☐	☐	☐	☐☐
November	☐	☐	☐☐	☐	☐	☐☐
December	☐	☐	☐☐	☐	☐	☐☐

SMOKING BEHAVIOUR *(Continued)*

	CIGARS			PIPE		
	Have you smoked Cigars at all during the following months?		If ***Yes***, How many per week?	Have you smoked the Pipe at all during the following months?		If ***Yes***, How many per week?
	YES	**NO**		**YES**	**NO**	
January	☐	☐	☐☐	☐	☐	☐☐
February	☐	☐	☐☐	☐	☐	☐☐
March	☐	☐	☐☐	☐	☐	☐☐
April	☐	☐	☐☐	☐	☐	☐☐
May	☐	☐	☐☐	☐	☐	☐☐
June	☐	☐	☐☐	☐	☐	☐☐
July	☐	☐	☐☐	☐	☐	☐☐
August	☐	☐	☐☐	☐	☐	☐☐
September	☐	☐	☐☐	☐	☐	☐☐
October	☐	☐	☐☐	☐	☐	☐☐
November	☐	☐	☐☐	☐	☐	☐☐
December	☐	☐	☐☐	☐	☐	☐☐
January	☐	☐	☐☐	☐	☐	☐☐
February	☐	☐	☐☐	☐	☐	☐☐
March	☐	☐	☐☐	☐	☐	☐☐
April	☐	☐	☐☐	☐	☐	☐☐
May	☐	☐	☐☐	☐	☐	☐☐
June	☐	☐	☐☐	☐	☐	☐☐
July	☐	☐	☐☐	☐	☐	☐☐
August	☐	☐	☐☐	☐	☐	☐☐
September	☐	☐	☐☐	☐	☐	☐☐
October	☐	☐	☐☐	☐	☐	☐☐
November	☐	☐	☐☐	☐	☐	☐☐
December	☐	☐	☐☐	☐	☐	☐☐

SECTION 2: DIETARY BEHAVIOURS

The questions in this section ask about your normal diet since *<month and year of last questionnaire>*.

2.1. Please indicate how often on average, since *<month and year of last questionnaire>*, you have eaten each of the food types that are listed below

	Average Use Since *<month and year of last questionnaire>*					
	Never or less than once per month	**1-3 per month**	**Once a week**	**2-4 per week**	**5-6 per week**	**At least once per day**
STAPLE FOODS						
Bread……..	☐	☐	☐	☐	☐	☐
Potatoes……..	☐	☐	☐	☐	☐	☐
Pasta…… (eg. Macaroni, spaghetti)	☐	☐	☐	☐	☐	☐
Rice…….	☐	☐	☐	☐	☐	☐
Noodles……...	☐	☐	☐	☐	☐	☐
Wheat…….. (eg. Whole grain bread)	☐	☐	☐	☐	☐	☐
Cereal……. (eg. Oats, bran, corn)	☐	☐	☐	☐	☐	☐
MEAT						
Meat (no organs)…… (eg. pork, steak, beef, lamb)	☐	☐	☐	☐	☐	☐
Organ Meat……. (eg. Liver, Heart, Kidney)	☐	☐	☐	☐	☐	☐
Chicken……	☐	☐	☐	☐	☐	☐
Other Poultry……... (eg. Goose, Duck, Pigeon)	☐	☐	☐	☐	☐	☐
FISH						
Dark fleshed fish……. (eg. mackerel, salmon, tuna, anchovies)	☐	☐	☐	☐	☐	☐
White fleshed fish…… (eg. cod, haddock, hake, halibut, sea bass, skate, sole, plaice)	☐	☐	☐	☐	☐	☐
Seafood…… (eg. Prawn, Crab, Lobster, Cockles, Winkles, Squid, Octopus, Mussels)	☐	☐	☐	☐	☐	☐
VEGETABLES						
Fruit Vegetables……. (eg. Tomato, Cucumber, Aubergine)	☐	☐	☐	☐	☐	☐

DIETARY BEHAVIOURS (Continued)

	Average Use Since *<month and year of last questionnaire>*					
	Never or less than once per month	1-3 per month	Once a week	2-4 per week	5-6 per week	At least once per day
VEGETABLES (Continued)						
Flower vegetables…… (eg. Broccoli, Cauliflower)	☐	☐	☐	☐	☐	☐
Leafy vegetables……. (eg. Spinach, Cabbage, Lettuce)	☐	☐	☐	☐	☐	☐
Stem vegetables……. (eg. Asparagus, Celery, Fennel)	☐	☐	☐	☐	☐	☐
Mushrooms……..	☐	☐	☐	☐	☐	☐
Bulbs……. (eg. Onion, Garlic, Leek, Shallot)	☐	☐	☐	☐	☐	☐
Roots…… (eg. Beetroot, Swede, Carrot, Parsnip)	☐	☐	☐	☐	☐	☐
FRUIT						
Citrus Fruits……. (eg. Orange, Lemon, Lime, Grapefruit)	☐	☐	☐	☐	☐	☐
Stone Fruits……. (eg. Plum, Apricot, Peach, Cherry)	☐	☐	☐	☐	☐	☐
Soft Fruits……. (eg. Raspberry, Strawberry, Redcurrant, Blackberry)	☐	☐	☐	☐	☐	☐
Fleshy Fruits…… (eg. Apple, Pear, Banana, Pineapple)	☐	☐	☐	☐	☐	☐
Vine Fruits…… (eg. Grape, Melon, Cantaloupe)	☐	☐	☐	☐	☐	☐
DAIRY						
Cream……...	☐	☐	☐	☐	☐	☐
Butter / Margarine……..	☐	☐	☐	☐	☐	☐
Yogurt……..	☐	☐	☐	☐	☐	☐
Cheese ……	☐	☐	☐	☐	☐	☐
Egg ……..	☐	☐	☐	☐	☐	☐
OTHER FOODS						
Pulses……... (eg. Pea, Bean, Lentil)	☐	☐	☐	☐	☐	☐
Nuts and Seeds……	☐	☐	☐	☐	☐	☐
Soy/Tofu products…… (eg. Soy milk, Tofu, Soya meat)	☐	☐	☐	☐	☐	☐
Sweets and snacks…… (eg. Crisps, cakes, ice cream, chocolate)	☐	☐	☐	☐	☐	☐

FLUID INTAKE

2.2. Please indicate how often, *<month and year of last questionnaire>*, you have drunk one measure each of the types of drinks that are listed below.

		Average Use Since <month and year of last questionnaire>						
	Measure	Never or less than one measure per month	1-3 per month	One a week	2-4 per week	5-6 per week	At least one per day	How many per day?
ALCOHOLIC DRINKS								
Wine or champagne……	1 small glass	☐	☐	☐	☐	☐	☐ →	☐☐
Fortified Wine……. (eg. Port, Sherry, Cinzano)	1 small glass	☐	☐	☐	☐	☐	☐ →	☐☐
Beer……. (eg. Beer, Lager, Stout)	1 Pint	☐	☐	☐	☐	☐	☐ →	☐☐
Cider……	1 Pint	☐	☐	☐	☐	☐	☐ →	☐☐
Spirits…….. (eg. Gin, Brandy, Rum, Vodka, Whisky)	1 pub measure (25cl)	☐	☐	☐	☐	☐	☐ →	☐☐
Liqueurs…….. (eg. Tia Maria, Cointreau, Baileys, Grand Marnier)	1 pub measure (25cl)	☐	☐	☐	☐	☐	☐ →	☐☐
HOT DRINKS								
Coffee…….	1 cup	☐	☐	☐	☐	☐	☐ →	☐☐
Tea……..	1 cup	☐	☐	☐	☐	☐	☐ →	☐☐
Hot Chocolate……	1 cup	☐	☐	☐	☐	☐	☐ →	☐☐
Ovaltine / Horlicks……..	1 cup	☐	☐	☐	☐	☐	☐ →	☐☐
Soup……	1 Cup / Bowl	☐	☐	☐	☐	☐	☐ →	☐☐
SOFT DRINKS								
Fizzy pop…… (eg. Lemonade, Cola)	½ pint glass	☐	☐	☐	☐	☐	☐ →	☐☐
Pure fruit juice……. (eg. Orange, Apple, etc)	½ pint glass	☐	☐	☐	☐	☐	☐ →	☐☐
Fruit squash or cordial……..	½ pint glass	☐	☐	☐	☐	☐	☐ →	☐☐
Milk……..	½ pint glass	☐	☐	☐	☐	☐	☐ →	☐☐
Water ……..	½ pint glass	☐	☐	☐	☐	☐	☐ →	☐☐

SECTION 3: VITAMINS AND SUPPLEMENTS

The questions in this section ask about your use of vitamins and dietary supplements. If you are participating in the Randomised Trial connected with this research, we do not need you to tell us about the vitamins that you have been given as part of the trial.

3.1. Have you taken, any of the following vitamins or supplements since *<month and year of last questionnaire>*?

Type of Vitamin / Supplement	Yes	no	Unknown	What is the name of your medication?	Where do you buy this product?
Example Example Example Example Example Example					
Multi-vitamins	☐	☑	☐	***ABC Plus Tablets***	***Holland and Barrett***
Multi-vitamins	☐	☐	☐		
Folic Acid	☐	☐	☐		
Vitamin B	☐	☐	☐		
Vitamin C	☐	☐	☐		
Vitamin E	☐	☐	☐		
Iron pills	☐	☐	☐		
Cod liver oil	☐	☐	☐		
Magnesium	☐	☐	☐		
Zinc	☐	☐	☐		
Vitamin B12	☐	☐	☐		
Selenium	☐	☐	☐		
Chromium	☐	☐	☐		
Calcium	☐	☐	☐		
Other (1)	☐	☐	☐		
Other (2)	☐	☐	☐		

If you are taking any vitamins or supplements. Please bring the packet in with you on your next hospital visit

SECTION 4: MEDICATIONS

Please indicate which medications you have taken since *<month and year of last questionnaire>*. Where possible, please also record the name of the of the medication that you have taken

4.1. Have you taken any of the following medications since *<month and year of last questionnaire>*, regularly for a period of 1 month or more?

Type of Medicine	Yes	No	Unknown	What is the name of your medication?
Example Example Example Example Example Example				
NSAID's	☑	☐	☐	***Ibuprofen***
Pain killers				
Paracetamol	☐	☐	☐	
Aspirin	☐	☐	☐	
NSAID's (eg. Ibuprofen, Brufen, Diclofenac, Volterol)	☐	☐	☐	
Medicine for high cholesterol (eg. Simvastatin, Pravastatin, Atorvastatin)	☐	☐	☐	

4.2. Have you taken any of the following medications at any time since *<month and year of last questionnaire>*?

Type of Medicine	Yes	No	Unknown	What is the name of your medication?
Antidepressants, sleeping pills or sedatives	☐	☐	☐	
Chemotherapy	☐	☐	☐	
Immune Suppressants (eg. Steroid Tablets, Cyclosporin)	☐	☐	☐	
Inhaled Steroids	☐	☐	☐	
Women Only: Hormone replacement therapy (HRT)	☐	☐	☐	
Women Only: The contraceptive pill	☐	☐	☐	

SECTION 5: MEDICAL HISTORY

The questions in this section ask about medical conditions you might have had since *<month and year of last questionnaire>*.

5.1. Have you been diagnosed with an illness or medical condition other than your bladder cancer since <month and year of last questionnaire>.

Condition #1

Name of Condition: _____

Month of diagnosis: ☐☐ Month (eg. Jan = 01) ☐☐☐☐ Year (eg. 2005)

Condition #2

Name of Condition: _____

Month of diagnosis: ☐☐ Month (eg. Jan = 01) ☐☐☐☐ Year (eg. 2005)

Condition #3

Name of Condition: _____

Month of diagnosis: ☐☐ Month (eg. Jan = 01) ☐☐☐☐ Year (eg. 2005)

Condition #4

Name of Condition: _____

Month of diagnosis: ☐☐ Month (eg. Jan = 01) ☐☐☐☐ Year (eg. 2005)

Condition #5

Name of Condition: _____

Month of diagnosis: ☐☐ Month (eg. Jan = 01) ☐☐☐☐ Year (eg. 2005)

Condition #6

Name of Condition: _____

Month of diagnosis: ☐☐ Month (eg. Jan = 01) ☐☐☐☐ Year (eg. 2005)

SECTION 6: STANDARD GAMBLE

- **Only Suitable for Patients Undergoing Cystoscopic Surveillance**
- **Not to be included in reassessment following recurrence or progression**

In this section, we would like you to consider a made-up situation and tell us how you would respond if it were a real situation.

Imagine that there is a new test available which claims to predict whether you will remain free of bladder cancer. The new test does not require you to have any internal examination of your bladder but will simply test samples of your blood, urine or bladder tissue that have already been collected.

Your urologist advises that if you take this test today, you will not have to undergo yearly cystoscopy anymore for the rest of your life, although you will have all other follow-up and treatment just as you are now.

However, the new test may not be 100% accurate, and so there is a chance that your bladder cancer could come back even if the test says it won't. So by taking the new test, and not having regular cystoscopies, this inaccuracy may mean if your cancer does come back, it might be missed. There is no way of knowing which patients will be predicted correctly by this new test.

Your urologist offers you the choice between having the test and no more cystoscopies or to continue with regular cystoscopies. Your urologist will support whatever decision you make.

	YES	**NO**
6.1. Would you take the new test today if you knew that out of **1 thousand** patients …		
…the test correctly predicts no recurrence in all 1000 patients (i.e. 100% accurate)	☐	☐
…the test correctly predicts no recurrence for 999 patient but misses 1 (i.e. 99.9% accurate)	☐	☐
…the test correctly predicts no recurrence for 990 patients but misses 10 (i.e. 99% accurate).	☐	☐
…the test correctly predicts no recurrence for 970 patients but misses 30 (i.e. 97% accurate).	☐	☐
…the test correctly predicts no recurrence for 950 patients but misses 50 (i.e. 95% accurate).	☐	☐
…the test correctly predicts no recurrence for 900 patients but misses 100 (i.e. 90% accurate).	☐	☐

STANDARD GAMBLE *(Continued)*

- **Only Suitable for Patients Undergoing Cystoscopic Surveillance**
- **Not to be included in reassessment following recurrence or progression**

	YES	NO
…the test correctly predicts no recurrence for 800 patients but misses 200. (i.e. 80% accurate).	☐	☐
…the test correctly predicts no recurrence for 700 patients but misses 300 (i.e. 70% accurate).	☐	☐
…the test correctly predicts no recurrence for 600 patients but misses 400 (i.e. 60% accurate).	☐	☐
…the test correctly predicts no recurrence for 500 patients but misses 500 (i.e. 50% accurate).	☐	☐
…the test correctly predicts no recurrence for 400 patients but misses 600 (i.e. 40% accurate).	☐	☐
…the test correctly predicts no recurrence for 300 patients but misses 700. (i.e. 30% accurate)	☐	☐
…the test correctly predicts no recurrence for 200 patients but misses 800. (i.e. 20% accurate)	☐	☐
…the test correctly predicts no recurrence for 100 patients but misses 900. (i.e. 10% accurate)	☐	☐
…the test correctly predicts no recurrence for 0 patients but misses 1000. (i.e. 100% inaccurate)	☐	☐

SECTION 7: SOCIAL SUPPORT **- (to be completed by the patient)**

Here is a list of some things that other people do for us or give us that may be helpful or supportive. Please read each statement carefully and put a tick the box that is closest to your situation.

Example Example Example Example Example Example

	As much as I would like				Much less than I would like
I get enough vacation time……	☐	☑	☐	☐	☐

If you put a check where we have, it means that you get *almost* as much vacation time as you would like, but not quite as much as you would like.

		As much as I would like				Much less than I would like
7.1.	I have people who care what happens to me…….	☐	☐	☐	☐	☐
7.2.	I get love and affection……...	☐	☐	☐	☐	☐
7.3.	I get chance to talk to someone I trust about problems at work or with my housework ……	☐	☐	☐	☐	☐
7.4.	I get chance to talk to someone I trust about my personal and family problems……...	☐	☐	☐	☐	☐
7.5.	I get chance to talk about money matters ……..	☐	☐	☐	☐	☐
7.6.	I get invitations to go out and do things with other people ……..	☐	☐	☐	☐	☐
7.7.	I get useful advice about important things in life ...	☐	☐	☐	☐	☐
7.8.	I get help when I am sick in bed ……..	☐	☐	☐	☐	☐

SECTION 8: GENERAL HEALTH - **(to be completed by the patient)**

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number between 1 and 4 that best applies to you. There are no "right" or "wrong" answers. The answers that you provide will remain strictly confidential.

		Not at all	**A little**	**Quite a bit**	**Very much**
8.1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?.....	1	2	3	4
8.2.	Do you have any trouble taking a long walk?.....	1	2	3	4
8.3.	Do you have any trouble taking a short walk outside of the house?.....	1	2	3	4
8.4.	Do you need to stay in bed or a chair during the day?.....	1	2	3	4
8.5.	Do you need help with eating, dressing, washing yourself or using the toilet?.....	1	2	3	4

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
8.6.	Were you limited in doing either your work or other daily activities?.....	1	2	3	4
8.7.	Were you limited in pursuing your hobbies or other leisure time activities?.....	1	2	3	4
8.8.	Were you short of breath?.....	1	2	3	4
8.9.	Have you had pain?.....	1	2	3	4
8.10.	Did you need to rest?.....	1	2	3	4
8.11.	Have you had trouble sleeping?.....	1	2	3	4
8.12.	Have you felt weak?.....	1	2	3	4
8.13.	Have you lacked appetite?.....	1	2	3	4

GENERAL HEALTH *(Continued)* - (to be completed by the patient)

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
8.14. Have you felt nauseated?.....	1	2	3	4
8.15. Have you vomited?.....	1	2	3	4
8.16. Have you been constipated?.....	1	2	3	4
8.17. Have you had diarrhoea?.....	1	2	3	4
8.18. Were you tired?.....	1	2	3	4
8.19. Did pain interfere with your daily activities?.....	1	2	3	4
8.20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?.....	1	2	3	4
8.21. Did you feel tense?.....	1	2	3	4
8.22. Did you worry?.....	1	2	3	4
8.23. Did you feel irritable?.....	1	2	3	4
8.24. Did you feel depressed?.....	1	2	3	4
8.25. Have you had difficulty remembering things?.....	1	2	3	4
8.26. Has your physical condition or medical treatment interfered with your family life?.....	1	2	3	4
8.27. Has your physical condition or medical treatment interfered with your social life?.....	1	2	3	4
8.28. Has your physical condition or medical treatment caused you financial difficulties?.....	1	2	3	4

For the following questions, please circle the number between 1 and 7 that best applies to you

8.29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very Poor …….. Excellent

8.30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very Poor …….. Excellent

GENERAL HEALTH *(Continued)* **- (to be completed by the patient)**

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
8.31.	Did you have a fever?.....	1	2	3	4
8.32.	Did you feel ill or unwell?.....	1	2	3	4
8.33.	Did you have trouble arranging your life around repeated bladder treatment appointments (cystoscopies or instillations)?.....	1	2	3	4
8.34.	Did you worry about having repeated bladder treatment appointments (cystoscopies or instillations)?.....	1	2	3	4
8.35.	Were you worried about your health in the future?.....	1	2	3	4
8.36.	Did you worry about results of examinations or tests?	1	2	3	4
8.37.	Did you worry about possible future treatments?.....	1	2	3	4
8.38.	Did you have a bloated feeling in your abdomen?.....	1	2	3	4
8.39.	Have you had flatulence or gas?.....	1	2	3	4
8.40.	Have you felt physically less attractive as a result of your illness or treatment?.....	1	2	3	4
8.41.	Have you been dissatisfied with your body?.....	1	2	3	4
8.42.	Have you felt less feminine/masculine as a result of your illness or treatment?.....	1	2	3	4
PLEASE ANSWER QUESTIONS 8.42-8.49 ONLY IF YOU DO <u>NOT</u> HAVE A UROSTOMY					
8.43.	Have you had to urinate frequently **during the day**?	1	2	3	4
8.44.	Have you had to urinate frequently **at night**?.....	1	2	3	4
8.45.	When you felt the urge to pass urine, did you have to hurry to get to the toilet?.....	1	2	3	4
8.46.	Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?....	1	2	3	4
8.47.	Have you had difficulty going out of the house, because you need to be close to a toilet?.....	1	2	3	4
8.48.	Have you had any unintentional release (leakage) of urine?.....	1	2	3	4
8.49.	Have you had pain or a burning feeling when urinating?.....	1	2	3	4

GENERAL HEALTH *(Continued)* - (to be completed by the patient)

PLEASE ANSWER QUESTIONS 8.50-8.55 ONLY IF YOU HAVE A UROSTOMY

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
8.50. Has urine leaked from your urostomy bag?.....	1	2	3	4
8.51. Did you have problems with caring for your urostomy?	1	2	3	4
8.52. Was your skin around the urostomy irritated?.....	1	2	3	4
8.53. Have you felt embarrassed because of your urostomy?	1	2	3	4
8.54. Have you been dependent on others for caring for your urosomy?.....	1	2	3	4
8.55. Did you frequently have to change the urostomy bag?..	1	2	3	4

PLEASE ANSWER QUESTION 8.56 ONLY IF YOU HAVE USED A CATHETER DURING THE PAST WEEK

8.56. Have you had problems with self catheterization? (inserting a tube into the bladder to pass urine)……	1	2	3	4

During the past 4 weeks:	**Not at all**	**A little**	**Quite a bit**	**Very much**
8.57. To what extent were you interested in sex?.....	1	2	3	4
8.58. To what extent were you sexually active (with or without sexual intercourse)?.....	1	2	3	4
8.59. **For men only:** Did you have difficulty gaining or maintaining an erection?.....	1	2	3	4
8.60. **For men only:** Did you have ejaculation problems (e.g. dry ejaculation)? ……	1	2	3	4

Please answer the following 4 questions only if you have been sexually active during the past 4 weeks:	**Not at all**	**A little**	**Quite a bit**	**Very much**
8.61. Have you felt uncomfortable about being sexually intimate? ……	1	2	3	4
8.62. Have you worried that you may contaminate your partner during sexual contact with the bladder treatment that you have been receiving?.....	1	2	3	4
8.63. To what extent was sex enjoyable for you?.....	1	2	3	4
8.64. **For women only:** did you have a dry vagina or other problems during intercourse?.....	1	2	3	4

APPENDIX 4
SELENIB TREATMENT INFORMATION LEAFLET

SELENIB

TREATMENT INFORMATION LEAFLET

(Version 1.0 – August 2006)

Please keep this information leaflet in your possession whilst taking the treatments given to you as part of the SELENIB trial.

SELENIUM / SELENIUM PLACEBO

How to take the selenium/selenium placebo tablets:
Swallow 1 tablet with water per day during or after mealtimes. Do not take more than one tablet per day. If you forget to take the tablets, re-start taking them as soon as you remember, but do not try to catch-up by taking more than one tablet in a day.

What is in the selenium/selenium placebo tablet?
Each of the selenium/selenium placebo tablets given to you as part of the SELENIB trial are manufactured as 10mm round white tablets, packed in transparent blister packs with an aluminium membrane approved for use with food. The blister packs are contained in a cardboard box. Each box contains 180 tablets (6 x 30 blister packs).

One tablet contains either 200 microgrammes of organic selenium yeast or only inactive ingredients. The tablets are sugar and gluten free and are suitable for vegetarians.

The tablets also contain the following ingredients: Microcrystalline cellulose, dicalcium phosphate, anticaking agent, silicon dioxide, megnesium stearate, talc, glazing agent: hydroxypropyl methyl cellulose, colour: titanium dioxide.

How should selenium/selenium placebo tablets be stored?
Do not use after the expiry date shown on this pack. Store at room temperature, out of direct sunlight. Store in original packaging. Remember: keep all medicines out of the reach and sight of children.

Whilst taking the selenium/selenium placebo tablets:
Pregnant and lactating women should consult a doctor or their Urologist before using this product.

Side effects: Selenium tablets are generally well tolerated by the majority of people, however if it is taken in large doses it can sometimes cause the following side effects; nausea, upset stomach, fatigue, irritability, dermatitis, cough and cold, bronchitis, hair brittleness, hair loss, bad breath, dizziness and nail tenderness.

If you experience any side effects, please inform our researcher at your next hospital visit. **Serious side effects must be reported to immediately**. For contact details see overleaf.

SELENIB

TREATMENT INFORMATION LEAFLET

(Version 1.0 – August 2006)

Please keep this information leaflet in your possession whilst taking the treatments given to you as part of the SELENIB trial.

VITAMIN E / VITAMIN E PLACEBO

How to take the vitamin E/vitamin E placebo capsules:
Swallow 1 tablet with water per day during or after mealtimes. Do not take more than one tablet per day. If you forget to take the tablets, re-start taking them as soon as you remember, but do not try to catch-up by taking more than one tablet in a day.

What is in the vitamin E/vitamin E placebo capsules?
Each of the vitamin E/vitamin E placebo capsules given to you as part of the SELENIB trial are manufactured as size 10 oval gelatine capsules. The capsule is clear and the content is yellow oil. The capsules are packed in transparent blister packs with an aluminium membrane approved for use with food. The blister packs are contained in a cardboard box. Each box contains 180 capsules (6 x 30 blister packs).

One capsule contains either 200 International Units of Bio E-Vitamin (d-alpha-tocopherol) or only inactive ingredients. The capsules are yeast, sugar and gluten free.

The capsules also contain the following ingredients: soya bean oil, gelatine, glycerol.

How should vitamin E/vitamin E placebo capsules be stored?
The shelf life for the product is 4 years. For use by date see flap on treatment box. Store at room temperature, out of direct sunlight.

Whilst taking the vitamin E/vitamin E placebo capsules:
Vitamin E is generally well tolerated but may rarely cause the following symptoms; diarrhoea, abdominal pain, upset stomach, blurred vision, dizziness, fatigue and weakness.

Consult a doctor or your Urologist before using this product if:

- You are taking anticoagulation medications (e.g. warfarin) before starting taking the study treatment
- You have a known vitamin K deficiency as this increased the risk of bleeding with high intakes of vitamin E.
- Women only: You are pregnant or lactating

If you experience any side effects, please inform our researcher at your next hospital visit. **Serious side effects must be reported immediately**. For contact details please see below.

If you have any queries or concerns please contact our researcher <Name> on <Tel>.

If, in the case of an emergency, your doctor requires information about whether or not you are taking either selenium or vitamin E, please contact the your hospital pharmacist on <pharmacy telephone number>.

APPENDIX 5
SELENIB TREATMENT COMPOSITION

Treatment Name	Pharmaceutical form	Shelf Life (Years)	Formulation			
			Function	Composition	Weight	Weight %
Bio-E Vitamin svag	Clear soft gelatine capsule, size 5 minim, oval with light brown to amber oil	4	Vitamin	d-α-Tocopherol 1300 IU/g	154 mg	39,49
			Bulking agent	Soy Bean oil	116 mg	29,74
			Capsule shell	Gelatin	81 mg	20,77
			Humectant	Glycerol (E422)	39 mg	10,00
Bio-E Vitamin svag placebo	Clear soft gelatine capsule, size 5 minim, oval with light brown to amber oil	4	Bulking agent	Soy Bean oil	270 mg	69,23
			Capsule shell	Gelatin	81 mg	20,77
			Humectant	Glycerol (E422)	39 mg	10,00
			Colour	Ammonia Caramel (E150c) quantum satis	0,0 mg	0,00
Seleno-Precise	White coated, round biconvex tablet with a motar bossing on each side. (9,5mm)	5	Mineral	Selenium Yeast (SelenoPrecise yeast) 1200 ppm Se	167,0 mcg	43,72
			Bulking agent	Microcrystalline cellulose (E460)	110,0 mcg	28,80
			Firming agent	Dicalciumphosphate (E341)	91,0 mcg	23,82
			Firming agent	Silicon dioxide fine (E551)	5,0 mcg	1,31
			Glazing agent	Hypromellose (E464)	3,0 mcg	0,79
			Glazing agent	Talc (E553b)	2,0 mcg	0,52
			Anti-caking agent	Magnesium stearate (E470b)	2,0 mcg	0,52
			Colour	Titanium dioxide	2,0 mcg	0,52
Seleno-Precise placebo	White coated, round biconvex tablet with a motar bossing on each side. (9,5mm)	5	Mineral	Selenium Yeast placebo	250,0 mcg	61,12
			Bulking agent	Microcrystalline cellulose (E460)	80,0 mcg	19,56
			Firming agent	Dicalciumphosphate (E341)	65,0 mcg	15,89
			Firming agent	Silicon dioxide fine (E551)	5,0 mcg	1,22
			Glazing agent	Hypromellose (E464)	3,0 mcg	0,73
			Glazing agent	Talc (E553b)	2,0 mcg	0,49
			Anti-caking agent	Magnesium stearate (E470b)	2,0 mcg	0,49
			Colour	Titanium dioxide	2,0 mcg	0,49

APPENDIX 6
SELENIB ADVERSE EVENTS CHECKLIST

CANCER RESEARCH UK	**BLADDER CANCER PROGNOSIS PROGRAMME (BCPP)**	**SELENIB FOLLOW-UP** ADVERSE REACTIONS CHECKLIST Page 1 of 2

Patient Identifier: *eg: John Smith = SMIJO*	☐☐☐☐☐	Hospital Name:	_____
Date of Birth:	D D M M Y Y Y Y	Hospital No:	_____
Date of Follow-up:	D D M M Y Y Y Y	Follow-up Conducted By:	_____

ADVERSE REACTIONS (for grading please refer to attached NCI – CTC extract)

Have you experienced any of the following symptoms during the last six months?

1. **Nausea?** **(1)** Yes **(2)** No ☐ If ***YES*** please specify grade ☐
   Brief description of symptoms? ----------
   ----
2. **Upset stomach?** **(1)** Yes **(2)** No ☐ If ***YES*** please specify grade ☐
   Brief description of symptoms? ----------
   ----
3. **Fatigue / tiredness?** **(1)** Yes **(2)** No ☐ If ***YES*** please specify grade ☐
   Brief description of symptoms? ----------
   ----
4. **Irritability?** **(1)** Yes **(2)** No ☐ If ***YES*** please specify grade ☐
   Brief description of symptoms? ----------
   ----
5. **Dermatitis?** **(1)** Yes **(2)** No ☐ If ***YES*** please specify grade ☐
   Brief description of symptoms? ----------
   ----
6. **Cough and/or cold?** **(1)** Yes **(2)** No ☐ If ***YES*** please specify grade ☐
   Brief description of symptoms? ----------
   ----
7. **Bronchitis?** **(1)** Yes **(2)** No ☐ If ***YES*** please specify grade ☐
   Brief description of symptoms? ----------

CANCER RESEARCH UK	**BLADDER CANCER PROGNOSIS PROGRAMME (BCPP)**	**SELENIB FOLLOW-UP** ADVERSE REACTIONS CHECKLIST Page 1 of 2

Patient Identifier: *(eg John Smith = SMIJO)* ☐☐☐☐☐	**Centre:** _____	**Study Number:** ☐☐☐☐

8. Hair brittleness / loss? **(1)** Yes **(2)** No ☐ If ***YES*** please specify grade ☐
Brief description of symptoms? ----------
---

9. Dizziness? **(1)** Yes **(2)** No ☐ If ***YES*** please specify grade ☐
Brief description of symptoms? ----------
---

10. Nail tenderness? **(1)** Yes **(2)** No ☐ If ***YES*** please specify grade ☐
Brief description of symptoms? ----------
---

11. Diarrhoea? **(1)** Yes **(2)** No ☐ If ***YES*** please specify grade ☐
Brief description of symptoms? ----------
---

12. Abdominal pain? **(1)** Yes **(2)** No ☐ If ***YES*** please specify grade ☐
Brief description of symptoms? ----------
---

13. Blurred Vision **(1)** Yes **(2)** No ☐ If ***YES*** please specify grade ☐
Brief description of symptoms? ----------
---

14. Weakness? **(1)** Yes **(2)** No ☐ If ***YES*** please specify grade ☐
Brief description of symptoms? ----------
---

15. Other adverse event? **(1)** Yes **(2)** No ☐ If ***YES*** please specify grade ☐
Brief description of symptoms? ----------
---

16. Other adverse event? **(1)** Yes **(2)** No ☐ If ***YES*** please specify grade ☐
Brief description of symptoms? ----------

COMMON TOXICITY CRITERIA (Extracted from NCI CTC Version 3)				
This extract lists known side effects of high dose selenium and/or vitamin E. Please report any grade IV event immediately as an SAE (See section X.X of protocol for SAE reporting requirements)				
Grade	**I**	**II**	**III**	**IV**
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24hrs.	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated >24hrs.	Life-threatening consequences
Gastrointestinal symptoms	Mild	Moderate	Severe	Life threatening; disabling
Fatigue (asthenia, lethargy, malaise)	Mild fatigue over baseline	Moderate or causing difficulty performing some activities of daily living	Severe fatigue interfering with activities of daily living	Disabling
Irritability	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalisation indicated
Dermatitis / rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localised desquamation or other lesions covering <50% of body surface area	Severe, generalised erythroderma or macular, popular or vesicular eruption; desquamation covering ≥50% body surface area	Generalised exfoliative, ulcerative, or bullous dermatitis
Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or activities of daily living	
Bronchospasm / wheezing / “bronchitis”	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening
Hair loss / alopecia (scalp or body)	Thinning or patchy	Complete		
Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with activities of daily living	Interfering with activities of daily living	Disabling

COMMON TOXICITY CRITERIA (Extracted from NCI CTC Version 3)				
Grade	**I**	**II**	**III**	**IV**
Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with activities of daily living	
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with activities of daily living	Increase of ≥7 stools per day over baseline; incontinence; IV fluids >24hrs; hospitalisation; sever increase in ostomy output compared to baseline; interfering with activities of daily living	Life-threatening consequences (e.g. haemodynamic collapse)
Abdominal pain	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with activities of daily living	Severe pain; pain or analgesics severely interfering with activities of daily living	Disabling
Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with activities of daily living	Symptomatic and interfering with activities of daily living	Disabling
Muscle weakness, generalised or specific area (not due to neuropathy)	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with activities of daily living	Symptomatic and interfering with activities of daily living	Life-threatening; disabling
Other events to be reported immediately as SAE's				
Cerebrovascular ischaemia	N/A	Asymptomatic, radiographic findings only	Transient ischaemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs
Coagulation abnormalities / coagulopathy	INR 1 - 1.5 x upper limit of normal (ULN)	INR 1.5 – 2x ULN	INR >2x ULN	

Please refer to full length version of NCI CTCAE V3.0 for adverse events not listed.

APPENDIX 7
MOLECULAR MARKERS TO BE EXAMINED

FGFR3

FGFR3 belongs to a family of structurally related tyrosine kinase receptors encoded by four different genes, FGFR1-4.[193] The wild type FGFR3 gene is expressed in both normal urothelium and bladder TCC. van Rhijn et al demonstrated that FGFR3 mutations occurred in 34 of 53 pTa tumours, and did not occur in TCCs of stage pT1 or above. Furthermore, all tumours with FGFR3 mutations were grade 1 or 2 only. In addition, recurrence at 12 months was far more frequent in those patients whose initial tumours expressed the wild type FGFR3 gene (61% vs. 21%, p=0.004).[194] Similar results were also found by Billerey et al.[193] FGFR3 mutations thus appear to be associated with favourable prognostic features, and it is suggested that FGFR3-mutated TCCs shed cells less easily and/or have a lower proliferation rate than non-mutated tumours.[194] Interestingly, FGFR3 mutations and TP53 mutations appear to be mutually exclusive, defining separate pathways of transitional cell carcinogenesis.[195-196] We therefore hypothesise that the presence of FGFR3 mutations is an independent predictor of a lower risk of recurrence and progression.

EGFR

The epidermal growth factor receptor (EGFR) is a member of the tyrosine kinase receptor family, a group all encoded by the c-*erb*B oncogenes. It is the activation of the tyrosine kinase domain of EGFR that initiates signal transduction following ligand binding, with ligands including EGF, transforming growth factor-alpha (TGF-α), amphiregulin, betacellulin, heparin-binding EGF-like factor (HB-EGF), and epiregulin. Pathological expression of EGFR leads to uncontrolled cell proliferation, and also increased angiogenesis and reduced apoptosis.[197] Overexpression of EGFR in bladder cancer is widely-reported to be associated with high tumour stage, tumour progression, and poor clinical outcome.[197-198] Inhibition of EGFR activity is considered to be a way of improving the prognosis of patients with bladder cancer and tyrosine kinase inhibition is one approach that is currently being extensively studied in this and other malignancies.[197-199] The combined use of gefitinib ("Iressa", ZD1839), a small molecule tyrosine kinase inhibitor which targets the epidermal growth factor receptor, with radiotherapy significantly diminishes bladder cancer cell proliferation, both *in vitro* and *in vivo*, compared with either treatment modality used on its own.[200] We hypothesise that overexpression of EGFR is an independent predictor of the risk of progression.

pRB

Most antiproliferative signals utilise the retinoblastoma protein (pRB)[201], with hypophosphorylated pRB blocking proliferation.[202] Altered pRB expression is found to be associated with tumour progression and worse disease-free survival in a number of

studies.[203-206] We hypothesise that altered pRB expression is an independent predictor of the risk of progression.

p53

The p53 gene is the most common target of genetic alteration identified in human cancers, and cells with inactivated p53 have a selective growth advantage.[207] Normal p53 function can be lost in a number of ways but most commonly by loss of a chromosomal region containing one allele of the gene and a subtle mutation involving the other allele (found on chromosome 17p) [reviewed by Nakamura[208]]. p53 is considered to be the "guardian of the genome" as it can induce either apoptosis or DNA repair.[209] Following DNA damage, increased levels of p53 protein causes cell cycle arrest and subsequently induces apoptosis.[210-212] p53-target genes have a number of other physiological roles including inhibiting angiogenesis, ameliorating oxidative stress, and immuno-surveillance.[208] p53 protein is constitutively expressed in all cell types but does not accumulate due to its rapid degradation by the proteasome, the degradation initiated by Mdm2.[213] The majority of p53 mutations are stabilising, allowing p53 protein to accumulate and immunostain. Up to 10% of bladder tumours will have p53 gene mutations and approximately 66% of tumours have dysregulated p53 at the protein level, which is strongly related to tumour invasiveness. [214] Typically, p53 alterations are associated with advanced bladder cancers, although there may be a role early in transitional cell carcinogenesis as p53 deficiency predisposes the urothelium to hyperproliferation.[215]

The evidence supporting the role of abnormal p53 expression in urothelial carcinogenesis appears very strong [186,216-218], and that its effect has not been assessed in a multivariate manner with the other potentially important markers (except with pRB[186]). In this context, we therefore hypothesise that abnormal p53 expression is an independent predictor of recurrence and progression.

Our results will complement the combined retrospective analysis by The International Study Initiative on Bladder Cancer[219] (which does not include other markers).

Ki-67

Ki-67 expression (detected with the MIB-1 antibody) is a marker of tumour proliferation. In a study of 31 patients who had undergone radical cystectomy for bladder cancer Tsuji et al demonstrated that patients whose tumour samples had a high Ki-67 index (>32%) had a significantly worse prognosis than those with a lower index.[220] Liukkonen et al studied 207 patients with Ta/T1 bladder cancer followed up for 4.9 years. Using multivariate analysis they demonstrated that MIB-1 score was an independent predictor of progressive disease and cancer-specific survival.[221] Similarly, Pfister et al studied 319 patients with newly-diagnosed Ta/T1 bladder cancer and found that a Ki-67 index greater than 10% was an independent

predictor of tumour recurrence among patients with large tumours (> 3cm).[222] We hypothesise that the proliferative index, as assessed by Ki-67 expression stained with MIB-1, is an independent predictor of recurrence and progression.

VEGF

Vascular Endothelial Growth Factor (VEGF) is a pro-angiogenic signal[223], with sustained angiogenesis being an important factor in allowing proliferative lesions to increase their capability for growth and invasion. Sustained angiogenesis also appears to play an important role both early and late in bladder transitional cell carcinogenesis.[14] High expression of VEGF mRNA in 55 Ta/T1 bladder TCCs was associated with earlier recurrence and progression.[224] High pre-operative urinary VEGF levels are associated with recurrence.[225] We hypothesise that high expression of VEGF is an independent predictor of recurrence and progression.

CK20

Cytokeratins are components of the intermediate filaments of the cell cytoskeleton and are characteristic of epithelial cells.[226] In normal urothelium CK20 expression is restricted to the superficial umbrella cells and occasional intermediate cells. Loss of this restriction was demonstrated in 31 of 36 cases of urothelial dysplasia (86%), with positive expression in all layers of the urothelium.[227] A normal CK20 expression appears to be predictive of tumour non-recurrence. Harnden et al showed that out of 58 consecutive patients with non-invasive papillary bladder tumours 10 had a normal pattern of CK20 expression and none of these 10 tumours developed further recurrence during the median follow-up of 18 months. By contrast, 30 of 41 evaluable patients with tumours that showed abnormal CK20 expression (73%) developed further tumours, with a median time to a second tumour of 6 months.[228] Similarly, Alsheikh et al showed that in 16 patients with tumours with a normal pattern of CK20 expression, four experienced a recurrence, in contrast to the 15 of 30 patients with abnormal CK20 staining who experienced one or more recurrences.[229] We hypothesise that normal CK20 expression is an independent predictor of a lower risk of recurrence.

Other Markers

Alongside those markers named above (which have significant evidence to support their use in combination for predicting recurrence and progression), we will also investigate in smaller studies the expression of novel markers in paraffin-embedded tissues by IHC, in frozen tissue by Western blotting, PCR, gene expression studies and DNA/RNA sequencing, and in urine by mass spectrometry, ELISA, metabolomics, or DNA/RNA sequencing. These pilot studies may lead to the identification of new bladder cancer pathways, and ultimately new biomarkers or therapeutic targets worthy of further investigation and funding.

APPENDIX 8a
EXPERIMENTAL USE OF THE BCPP BIOLOGICAL MATERIALS AND CONFORMITY WITH THE HUMAN TISSUE ACT

Introduction

All of the BCPP biospecimens are stored in the Human Biomaterials Resource Centre (HBRC) at the University of Birmingham, a Human Tissue Act licensed facility (licence number 12358). These samples are hosted by HBRC with project-specific ethical approval. The analyses and research specified below represent these specified projects. Some of the planned analyses described below may be carried out by third parties (either by other academic institutions in a collaborative fashion, or by commercial organisations performing these analyses as a service or as a research collaboration). In such cases, the material may be transferred to these third parties but the research will be carried out in line with objectives detailed below.

Paraffin-Embedded Tissues

As outlined in Section 5, paraffin-embedded tissues will be utilised to construct tissue arrays for use in immunohistochemistry (IHC), screening for a panel of recognised molecular markers, in addition to more novel markers (the initial markers are described in Appendix 7). It is feasible, however, that IHC approaches may be superseded during the life of BCPP and our approach to the identification of prognostic and predictive markers may need to be amended.

In some instances, the volume of bladder tumour material within the paraffin block will be too small to enable the 5mm “Tru-Cut” cores to be taken to construct the tissue arrays. In this case, we will request individual paraffin section slides for use in conventional (non-tissue array) IHC.

Parraffin-embedded tissues will also be utilised for laser-assisted microdissection and DNA extraction for use in the PCR-SSCA (single-strand conformation analysis) screening for FGFR3 mutations (see Section 5 and Appendix 7). However, the yield of DNA with this technique can be variable and very low, and other tissue samples will need to be utilised for DNA extraction (e.g. snap-frozen fresh tissue).

In addition, we plan to extract RNA and DNA from the paraffin-embedded tissue. RNA will be used for RNA expression studies (eg. RT-PCR). Again, yields may be low so we plan to initially carry out pilot studies on sample sets, utilising our stored snap frozen tissue for comparison. We plan larger screens of DNA and RNA expression patterns if these extraction techniques prove to be sufficiently robust, focussing on the genes implicated in bladder cancer (such as those outlined in Section 5 and Appendix 7). Expression will be correlated with that seen in the linked frozen tissue (see below). This will provide important validation of this

technology in our laboratory, and may allow us to extend DNA and RNA studies to patients without stored frozen tissue.

DNA and RNA extracted in this way will be used for:

- Genomics to identify mutations, gene fusions, methylation status, and other DNA or RNA abnormalities. Platforms such as “next generation sequencing” will be utilised.
- Epigenomics to identify abnormalities in the epigenetic regulation of the genome (eg. DNA methylation, histone acetylation, microRNAs, etc). Platforms such as pyrosequencing, *Illumina* Infinium methylation array and *Sequenom* MassARRAY will be utilised, as well as others.

Snap Frozen Fresh Tissue

For extracting DNA and RNA for molecular analyses, snap frozen fresh tissue generally gives reliable and high-quality yields above and beyond those obtained from paraffin-embedded tissues. Initial pilot studies will compare these yields so that the techniques outlined above can be refined. As part of this process, DNA will therefore be extracted for use in the PCR-SSCA screening for FGFR3 mutations (see Section 5 and Appendix 7) and compared with the results obtained from paraffin-embedded tissues. In a similar fashion, RNA will be extracted from these tissues for use in RNA expression studies, such as real-time RT-PCR (reverse transcriptase polymerase chain reaction) comparing tumour tissue mRNA levels for EGFR, pRB, p53, Ki-67, VEGF, and CK20 (and some of those markers listed in Appendix 7 above) with the corresponding protein expression levels detected by IHC.

In the future, these tissues will be utilised for further genomic, proteomic and metabolomic analyses within our laboratories, including “next generation sequencing”. Recent years have seen increasing interest in and understanding of the cancer genome.[230] A number of different types of genomic changes are at work in all cancers, including point mutations, gene fusions, regulatory changes, deletions and copy number changes. At heart, cancer originates from changes in DNA, so tumour-specific DNA sequences make attractive candidate biomarkers. The arrival of high-throughput or “next generation” sequencing platforms means that the investigation of the cancer genome is more straightforward; several dozen proof-of-principle papers are available in the scientific literature, showing how these technologies can be used to detect SNPs and gene fusions associated with human cancers (although none of them so far have focused on bladder cancer). Such techniques (whole genome sequencing or transcriptome sequencing) can be used to sequence the genomes of individual cancers, thereby facilitating the discovery of tumour-specific mutations or gene fusions, etc. This then primes the creation of more simple assays to detect specific disease-related mutations or gene fusions, assays that can also be used to detect and quantify free tumour DNA in the

patient's circulation[231], or even urine. Viral incorporation into tumour DNA may also be an important prognostic factor[232], and DNA- and RNA-based approaches will permit this to be investigated.

We intend to utilise the high-throughput deep sequencing platforms that are available at the University of Birmingham and the West Midlands Regional Genetics Laboratory (and in some instances, external providers of sequencing services) to investigate the bladder cancer genome. With the falling costs of these platforms, there is the potential to sequence a large number of our biospecimens. Whole blood samples will be used as germline DNA controls.

In addition, epigenomics will be utilised to identify abnormalities in the epigenetic regulation of the genome (e.g. DNA methylation, histone acetylation, microRNAs, etc). Platforms such as pyrosequencing, *Illumina* Infinium methylation array and *Sequenom* MassARRAY will be utilised, as well as others.

The mechanical properties of bladder tumours are also of significant interest for the development of new surgical techniques and instruments. Having completed a study on the viscoelastic properties of porcine bladder tissue (which is a reasonable model for normal human bladder tissue), we aim to determine the viscoelastic properties of human bladder cancers. The differing properties between bladder cancer and normal bladder may permit the design of new devices to remove only tissue of certain mechanical properties. In addition, computer models of the bladder can be simulated (such as multi-physics models of TURBT) to determine the path of exfoliated cancer cells during surgery; currently only limited mechanical properties are known, which make computational studies difficult. To achieve this, we will work with bio-medical engineers at the University of Birmingham and elsewhere, and testing will involve compressing samples to measure mechanical properties (using a Bose 3200 materials testing machine, *Bose Corporation, ElectroForce Systems Group, Minnesota, USA*).

<u>Whole Blood</u>

Our whole blood samples will predominantly be utilised for the extraction of DNA. The DNA will then be used as "normal" germline controls in screening for FGFR3 mutations. In the future, these samples will be used for further analyses including:

- The detection of circulating micrometastases.
- The detection of cell-free tumour DNA.
- Next generation sequencing (germline DNA controls, as described above).
- Genome-wide association studies and single nucleotide polymorphism (SNP) studies (as part of national and international collaborations).

For example, Teo *et al* (Ann Oncol (2014) 25 (4): 877-883) reported an association between cancer specific survival and the presence of the minor A allele at the MRE11 single nucleotide polymorphism, rs1805363, in patients with muscle invasive bladder cancer. The presence of the minor A allele acted in line with a gene dosage effect and was also found to be linked to an increased expression of MRE11 isoform 2 over isoform 1, compared to wild type. Therefore, germline DNA samples from bladder cancer patients plus subsequent sections of slides from selected matching fresh-frozen tumour will be analysed to corroborate these data. The germline DNA will be sequenced across the MRE11 rs1806353 site to establish the presence or absence of the A minor allele at the site. Matched fresh frozen tissue will then undergo RNA extraction in order to quantify the ratio of the MRE11 isoform 1 and MRE11 isoform 2 mRNA expressed in cells, which in turn can be related back to patient survival data and patient rs1805363 status.

Serum

Stored serum will be used for analysis of protein and phospho-protein expression patterns. This will occur in two ways: we plan to examine serum for expression of known biomarkers (see Table 1a below); in addition to ELISAs, we will employ broad spectrum screening techniques (such as SELDI-TOF and MALDI-TOF mass spectrometry, and NMR metabolomics) to detect novel biomarkers for bladder cancer detection, prediction of prognosis or treatment response, or for monitoring response to therapy. Furthermore, circulating tumour DNA extracted from serum samples can be utilised as a liquid biopsy for the detection of advanced disease and for the development of personalised biomarkers.

Urine

Our urine samples are stored after centrifugation to remove cellular material and debris. We plan to examine the collected pelleted material and cell-free DNA in the supernatant for expression/mutations/copy number changes of the genes listed in Section 5 and Appendix 3, and others, using a variety of protein, DNA and RNA detection techniques such as PCR and next generation sequencing. We also intend to use these urine DNA samples to investigate genetic and epigenetic pathways (e.g. methylation and histone acetylation) using platforms such as pyrosequencing and *Sequenom* MassARRAY.

The urine supernatant will be examined for the markers listed in Appendix 7 above and Table 5a below, together with a programme of marker discovery using mass spectrometry and metabolomics techniques (such as SELDI-TOF and MALDI-TOF, and NMR metabolomics) with the intention of developing multiplex biomarker assays (utilising gas chromatography or ELISAs) for the diagnosis and monitoring of bladder cancer (including volatile organic compounds detectable in the gas emitted from urine samples). The detection and analysis of

cell-free tumour DNA is also feasible in urine samples and we will explore the potential of urinary cell-free DNA as a diagnostic, prognostic or predictive biomarker.

Toenail clippings

These will be used to measure body selenium content to assess the possible role of this mineral in both tumorigenesis and response to therapeutic intervention in the linked SELENIB trial.

Table 5a: Known bladder serum or urine protein cancer biomarkers

Protein	***Assay availability***
NMP22	ELISA
BTA	ELISA
Cytokeratins 8, 18,19 and 20	ELISA
Survivin	ELISA
Hyaluronic acid-hyaluronidase	ELISA
VEGF	ELISA
CA 19-9	ELISA
Fibrin/FDP	ELISA
Soluble Fas	ELISA
BLCA-4	antibody
Soluble E-cadherin	ELISA
TATI	ELISA
Calreticulin	ELISA
BLCA-1	ELISA
BTF	ELISA
Timp-2	ELISA
MMP 9	ELISA
NMP52	ELISA
Timp-1	ELISA
MMP 2	ELISA
Prothymosin-α	antibody
Reg-1	ELISA
M2-PK	ELISA

APPENDIX 9
SITE PARTICIPATION FORM

Responsible Urologist (Principal Investigator): …………………………………………

Centre Name: ……………………………………………………………………..

Address: ……………………………………………………………………..

……………………………………………………………………..

Tel: ……………………………….. Fax: ………………………………….

E-mail: ……………………………………………………………………..

- ❖ We want to participate in the Bladder Cancer Prognosis Programme (BCPP)
- ❖ We will enter all patients meeting the BCPP eligibility criteria
- ❖ We will undertake to respect the BCPP protocol, but our medical responsibility takes precedence over the protocol
- ❖ We will provide all of the necessary information and specimens

(Please provide a name and signature for each of the clinical team members listed below. This list should include all other Urologists at your centre)

<u>All other Urologists:</u>

1. Name: ………………………………… Signature: ,,,

2. Name: ………………………………… Signature: ,,,

3. Name: ………………………………… Signature: ,,,

4. Name: ………………………………… Signature: ,,,

5. Name: ………………………………… Signature: ,,,

6. Name: ………………………………… Signature: ,,,

(Continue on another sheet if necessary)

Pathologist: Name: …………………………….. Signature: …………………………...

Oncologist: Name: …………………………….. Signature: …………………………..

<u>Please return this form to:</u> The BCPP Study Office, Room G08, Public Health Building, Department of Public Health and Epidemiology, The University of Birmingham, B15 2TT

APPENDIX 10
Clinical Study Site Agreement – SELENIB

THE UNIVERSITY
OF BIRMINGHAM

CLINICAL STUDY SITE AGREEMENT

Between

THE UNIVERSITY OF BIRMINGHAM

and

<<CENTRE>>

relating to the clinical study known as
"SELENIB"

Study Acronym	SELENIB
Protocol Title	Bladder Cancer Prognosis Programme
Eudract No	2005-003021-19
LREC/MREC Ref	06/MRE04/65
UoB Sponsor No	RG_05-088
Chief Investigator	Dr Rik Bryan

THIS AGREEMENT is made the day of 200_
BETWEEN:

(1) **THE UNIVERSITY OF BIRMINGHAM** of Edgbaston Birmingham B15 2TT ("the University")

(2) [ ] of [ ] ("the Centre")

1. BACKGROUND

A) The University is leading the Study for which it has taken on the role of sponsor

B) The University wishes to engage the Centre to undertake part of the Study subject to the terms and conditions on the part of the Centre as set out in this Agreement

C) The Centre intends to appoint <<NAME>>, [an employee of the Centre/who holds an honorary contract with the Centre], as Site Principal Investigator for the Study

2. DEFINITIONS

2.1 "Chief Investigator"	means Dr Rik Bryan of the Department of Public Health and Epidemiology.
2.2 "Intellectual Property Rights"	means rights in any patent registered or unregistered trademark, trade and business name, domain name, know-how, together with any registered or unregistered design right, copyright, database rights and any other industrial or commercial monopoly rights which now subsist or may in the future subsist in any part of the world together with rights to apply for the registration of such rights
2.3 "the Protocol"	means the protocol for the Study entitled "SELENIB" as amended by the University from time to time
2.4 "the Study"	means the multi-centre clinical study initiated by the University and described in the Protocol of which brief details are set out below:

Study Acronym	SELENIB
Protocol Title	Bladder Cancer Prognosis Programme
Eudract No	2005-003021-19
LREC/MREC Ref	06/MRE04/65
UoB Sponsor No	RG_05-088
Chief Investigator	Dr Rik Bryan

3. COMMENCEMENT

This Agreement shall come into force on the date hereof and shall continue in force until completion by the Centre of its part of the Study or unless terminated in accordance with the terms of this Agreement

4. THE UNIVERSITY

The University shall act as Sponsor for the Study under the Research Governance Framework for Health and Social Care and/or the Research Governance Framework for Health and Community Care (as appropriate) and the Medicines for Human Use (Clinical Trials) Regulations 2004.

5. THE CENTRE

The Centre shall:

5.1 ensure that the Site Principal Investigator and his or her team are properly qualified trained and skilled to perform the clinical procedures required by the Study

5.2 ensure that the Study and related activities at the Centre are carried out in accordance with the requirements of the Research Governance Framework for Health and Social Care and/or (as appropriate), the Medicines for Human Use (Clinical Trials) Regulations 2004, the Data Protection Act 1998, the Protocol, and the Principles of Good Clinical Practice

5.3 ensure that the Site Principal Investigator and his or her team comply with the requirements on the reporting of Serious Adverse Events and Serious Adverse Reactions described in the Protocol and as may be required under the Medicines for Human Use (Clinical Trials) Regulations 2004

5.4 ensure that adequate facilities and support are available to the Site Principal Investigator for the proper performance of the Study at the Centre

5.5 ensure that, where required, suitable arrangements are made for the storage, labelling and subsequent disposal of trial drugs used in connection with the Study

5.6 ensure that no clinical trial subject shall be recruited into the Study at the Centre until the Centre is satisfied that all relevant regulatory and ethics committee approvals have been obtained

5.7 assist the University with any audits or monitoring if reasonably requested.

6. THE SITE PRINCIPAL INVESTIGATOR

6.1 The Centre shall procure the services of << Site PI Name>> to act as Site Principal Investigator.

6.2 The Centre shall ensure that the Site Principal Investigator completes the Declaration attached to this Agreement as Schedule A.

6.3 In the event that the Site Principal Investigator is unable or unwilling to continue in this role, the Centre may nominate a replacement to serve as Site Principal Investigator. In the event that no suitable replacement acceptable to the University and the Chief Investigator is found, then the University may terminate this agreement and suspend the Study at the Centre.

7. INTELLECTUAL PROPERTY & PUBLICATION

7.1 Any inventions discoveries ideas improvements devices products know-how and the like whether patentable or not and any copyright material contained in the Protocol and any amendments thereto shall belong to the authors of the Protocol or their employers. Any further developments improvements devices know-how and the like ("New Inventions") and copyright material that the Site Principal Investigator, the Centre its staff or agents make invent or produce during the course of the Study and any Intellectual Property Rights relating to such inventions or copyright material shall belong to and vest in the Centre. The University shall be

accorded a free licence to use such Intellectual Property Rights and copyright material in its own research and teaching.

7.2 It is agreed that the University shall publish the results of the full Study and that the Centre and the Site Principal Investigator shall not publish the results of the Study carried out at the Centre without the prior permission in writing of the University (which shall not be unreasonably withheld) and in any case not prior to the publication of the results of the full Study.

7.3 Each party shall keep confidential all information disclosed to it by another party pursuant to or for the purposes of this Agreement and shall not disclose it to any person

8. WARRANTIES AND INDEMNITY

8.1 The Centre shall maintain all proper insurance relevant to its activities in the Study including (but without prejudice to the generality of the foregoing):

8.1.1 If NOT an NHS Trust

i) professional indemnity insurance

ii) public liability insurance (which shall include cover for negligent acts or omissions on the part of the Centre or its employees servants or agents)

8.1.2 If an NHS Trust, NHS Indemnity under HSG(96)48 or MEL(2000)18 against claims arising as a result of clinical negligence by the Centre or its employees, honorary employees, servants or agents brought by or on behalf of clinical trial subjects recruited to the Study

8.2 The Centre shall provide to the University such evidence of the Centre's insurance cover maintained pursuant to clause 8.1 above as the University shall from time to time reasonably request

8.3 The Centre shall indemnify the University against all demands claims losses or costs arising due to the negligent act or omission of the Centre or its employees, honorary employees, servants or agents in the course of or in connection with the Study

8.4 The University is under no obligation to indemnify the Centre against any claims arising from the conduct of the Study at the Centre

8.5 As Sponsor the University is responsible for the general conduct of the study and shall indemnify the Centre against any claims arising from any negligent act or omission by the University in fulfilling the Sponsor role in respect of the Study.

9. TERMINATION

This Agreement may be terminated by the either party:

9.1 Immediately by notice in writing in the event that:

9.1.1 the defaulting party (in the reasonable opinion of the terminating party) is in material breach of any of its obligations under this Agreement;

9.1.2 either party is unable to continue the Study for reasons beyond its control including (but without prejudice to the generality of the foregoing) the loss of funding, withdrawal of ethical approval, withdrawal of approval by the Medicines and Healthcare products Regulatory Agency (MHRA), or the unavailability of the Chief Investigator or the Site Principal Investigator to supervise the Study

9.2 at any time by not less than one month's prior written notice to the other party

10. GENERAL

10.1 This Agreement shall be governed by English Law

10.2 All disputes differences and questions which at any time arise between the parties in connection with this Agreement or its subject matter shall be referred to a single arbitrator in accordance with the Arbitration Act 1996

10.3 Nothing in this Agreement confers or purports to confer on any third Party any right to enforce any term of this Agreement.

Signed for and on behalf of the **Centre**
Name ……..
Title…….

Signature……..

Signed on behalf of
The University of Birmingham

Name ……..
Title…….

Signature……..

SCHEDULE A

SITE PRINCIPAL INVESTIGATOR DECLARATION

I, ……., as Site Principal Investigator for the SELENIB study at <<Centre Name>> declare that

1. I am free to participate in the Study, and am not restricted by any third party obligations which would interfere with my conducting of the Study
2. I have considered the facilities required for the Study, and am satisfied that the Centre can and will continue to make adequate facilities available for the proper performance of the Study
3. I shall conduct the Study in accordance with the Research Governance Framework for Health and Social Care, the Data Protection Act 1998, the Protocol and the Principles of Good Clinical Practice
4. I shall conform to the requirements for reporting Serious Adverse Events and Serious Adverse Reactions as described in the Protocol and in any event shall notify the University forthwith upon receiving notification of such an event
5. I shall use all reasonable efforts to ensure that the data collected and reported to the Chief Investigator are accurate and complete
6. I shall assist with audits of the conduct of the Study whether undertaken by the University or a regulatory body
7. I consent to the University holding my name and other relevant details on the University's database for the purpose of communicating with me in relation to the Study and any future or proposed clinical study

Signed by the **Site Principal Investigator**

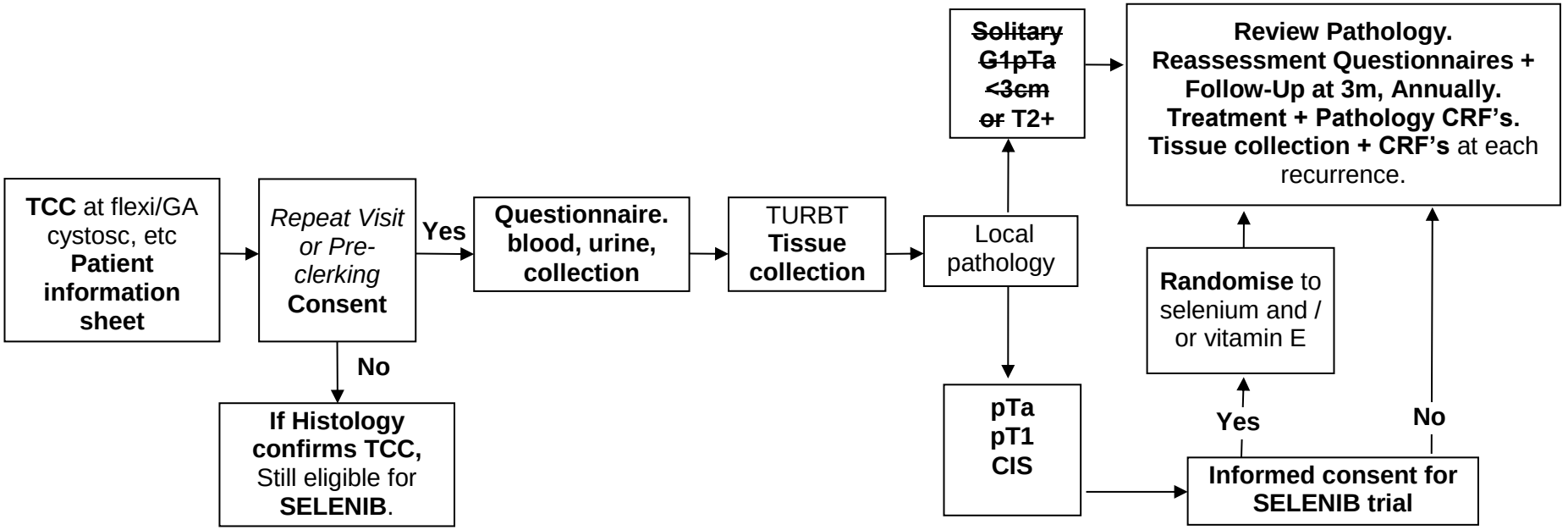
Name ……..

Title…….

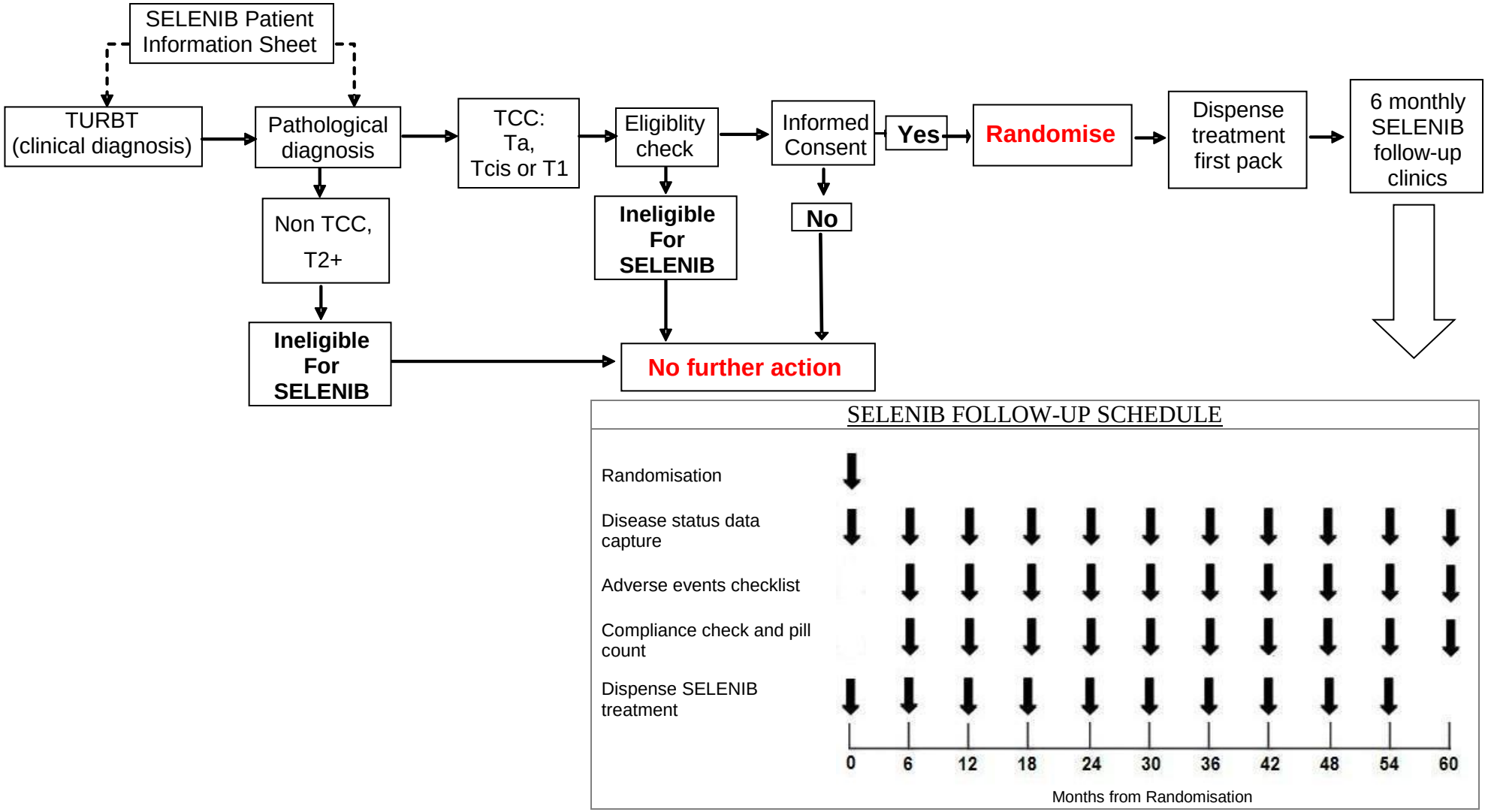
Signature……

APPENDIX 11
BCPP PATIENT PATHWAY

Figure 5: BCPP patient pathway



APPENDIX 12
FIGURE 6: SELENIB PATIENT PATHWAY



APPENDIX 13
SCHEDULE OF CRF RETURN

Form Number	Form Name	Enter / Return by
Form 1a	BCPP Registration	At time of obtaining consent
Form 1b	SELENIB Randomisation	At time of obtaining consent
Form 3a	TURBT	Within 2 weeks of surgery
Form 3b	Cystectomy	Within 2 weeks of surgery
Form 3c	Re-resection/Pathology	Not specified
Form 4a/b	Local Pathology Parts A & B	Within 2 weeks of surgery (This must be prior to SELENIB randomisation)
Form 5	MDT	Not specified
Form 6a	Intravesical Treatment	Not specified
Form 6b	Oncology Treatment	Not specified
Form 7a/b	Follow-up Form	Within 1 week of follow-up visit
Form 7c	SELENIB Follow-up Form	Within 1 week of follow-up visit
Form 8	SAE Form	Within 24 hours of detection
Form 9	Death Notification	Within 24 hours of detection
Form 10a	Completion	Not specified
Form 10b	Withdrawal	Within 1 week of withdrawal
Form 11	Recurrence / Progression Form including pathology	Not specified
Form 12	Relapse Cystectomy Form including pathology	Not specified
Form 14a	Relapse Treatment Form	Not specified
Form 14b	Relapse/Progression Intravesical Treatment	Not specified

APPENDIX 14
TOENAIL COLLECTION PROTOCOL

TO BE PRINTED ON HOSPITAL LETTERHEADED PAPER.

<Patient Title> <Patient Surname>
<Patient Address 1>
<Patient Address 2>
<Patient Address 3>
<Patient Address 4>
<Patient Address 5>
<Patient Post Code>

Dear <Patient Title> <Patient Surname>

RE: Bladder Cancer Prognosis Programme – toenail collection request

We would like to thank you once again for taking part in the Bladder Cancer Prognosis Programme. As explained by our researcher we have asked you to collect samples of your toenails and bring them back to us at your next hospital visit.

Why use toenails?
Many of the minerals that you need for good health find their way from your diet into parts of your body such as your hair and nails. Nails can therefore provide a painless and easy way of investigating the levels of these various natural minerals contained within the body. Toenails are usually covered up and are therefore less exposed to chemicals and other substances than hair or fingernails.

As part of the Bladder Cancer Prognosis Programme we would like to collect clippings from **all of your toenails**, so that we can look at the levels of these minerals amongst people such as yourself who have bladder cancer or a bladder abnormality. The toenail samples will be used for the purpose of current and future laboratory research.

Collection of your toenails for the Bladder Cancer Prognosis Programme
We would like you to read the attached instructions carefully, then to follow the instructions step by step. Please **do not** collect any nail clippings if your GP has advised you not to cut your own nails, if you are receiving treatment for the inflammation of blood vessels, if you are taking medication for high blood pressure (e.g. Warfarin) or if you are a diabetic.

If you have any queries or concerns, please telephone our local researcher on < mobile>.

Once you have collected the toenails, please bring them back to our researcher at the hospital, when you attend for your next appointment on <date>.

Thank you again for your continued participation.

Yours sincerely

<Urologist>

SPECIMEN NO: ☐☐☐☐☐

BLADDER CANCER PROGNOSIS PROGRAMME

Cancer Research UK Bladder Cancer Group

Toenail Instruction Collection Leaflet

CONFIDENTIAL

VERSION: FINAL 2.0 November 2009

PLEASE DESTROY PREVIOUS VERSIONS

A programme of research

Conducted by: *Funded by:*

UNIVERSITY OF BIRMINGHAM

CANCER RESEARCH UK

Part of the Bladder Cancer Prognosis Programme asks for you to collect samples of your toenails and send them to us.

Why Collect Toenail Clippings?
The reason that we ask for these is that many of the minerals that you need for good health find their way from your diet into parts of your body such as your hair and nails. Nails can therefore provide a painless and easy way of investigating the levels of these various natural minerals contained within the body. Toenails are usually covered up and are therefore less exposed to chemicals and other substances than hair or fingernails.

As part of the Bladder Cancer Prognosis Programme we would like to collect clippings from **all of your toenails**, so that we can look at the levels of these minerals amongst people such as yourself who have bladder cancer or a bladder abnormality. The toenail samples will be used for the purpose of current and future laboratory research.

Collection of your toenails for the Bladder Cancer Prognosis Programme
We would like you to read the attached instructions carefully, then to follow the instructions step by step. Please **do not** collect any nail clippings if your GP has advised you not to cut your own nails, if you are receiving treatment for the inflammation of blood vessels, if you are taking medication for high blood pressure (e.g. Warfarin) or if you are a diabetic.

If you have any queries or concerns, please telephone the Study Office on 0121 414 3024

Once you have collected the toenails, please send them back to us, following the attached instructions in the enclosed pre-paid (Freepost) envelope.

Thank you again for your continued participation.

Please read and carefully follow the instructions below. You may need to ask a family member or friend to help you.

First of all, please answer the following questions by circling either Yes or No.

1. Are you currently receiving treatment for inflamed blood vessels?	**YES / NO**
2. Are you taking tablets to thin your blood (e.g. Warfarin)?	**YES / NO**
3. Are you a diabetic?	**YES / NO**
4. Has your GP advised you not to cut your nails (for any reason)?	**YES / NO**

If you have answered **YES** to **any** of the above questions, **do not** collect any nail clippings and tell your research nurse at your next appointment.

If you have answered **NO** to **all** of the above questions, collect your toenails by following the instructions below;

Instructions

1. The toenail clippings should be cut immediately after bathing or showering using nail clippers or nail scissors routinely used for that purpose. Any nail polish on the nails should be removed with nail polish remover prior to bathing or showering.
2. After bathing or showering, take care to thoroughly rinse your feet to remove soap and shampoo from the nails. Use a soft nail brush to remove any debris from under the nails. Dry the nails with a tissue or towel.
3. Using a clean pair of nail scissors or nail clippers, carefully trim the nail straight across, to a comfortable length, so that the nail is level with the ends of the toes.
4. **DO NOT** cut down the sides of the nail. File the edges of the toenails smooth with an emery board.
5. Ensure, where possible, that you have taken clippings from every toe.
6. If you are **UNABLE** to obtain toenail clippings or if your toenails are not long enough to clip, you can alternatively collect all of your fingernail clippings in the same way as described above. Fingernails should only be collected where toenail collection is impossible.

Please telephone the Study Office on 0121 414 3024 if you are unable to collect either toenail or fingernail clippings for any reason.

(Continues on next page)

Instructions *(continued from previous page)*

7. Put the toenail clippings into the plastic bag provided and seal the bag.
8. Tick the boxes on the diagram page to indicate which toes (or fingers) you have taken clippings from
9. Fold up this instruction leaflet by folding it in half, then in half again.
10. Put the plastic envelope and the folded instruction leaflet into the paper envelope.
11. Peel off the paper backing of the self adhesive strip and stick down the envelope flap.
12. Write the date that you cut your nails on the front of the paper envelope in the space provided

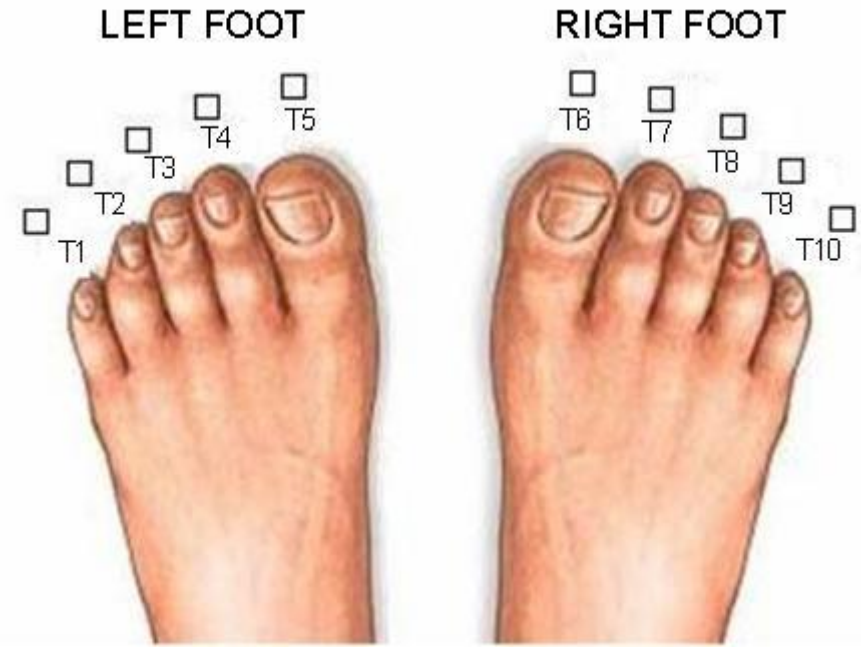
CHECK LIST

Check that it is OK for you to clip your toenails by answering the first 4 questions on the toenail collection instructions page. If you answered **YES** to **any** of the questions - do not collect any nail samples and tell your research nurse at your next appointment.but return this paperwork to the study office in the envelope provided.

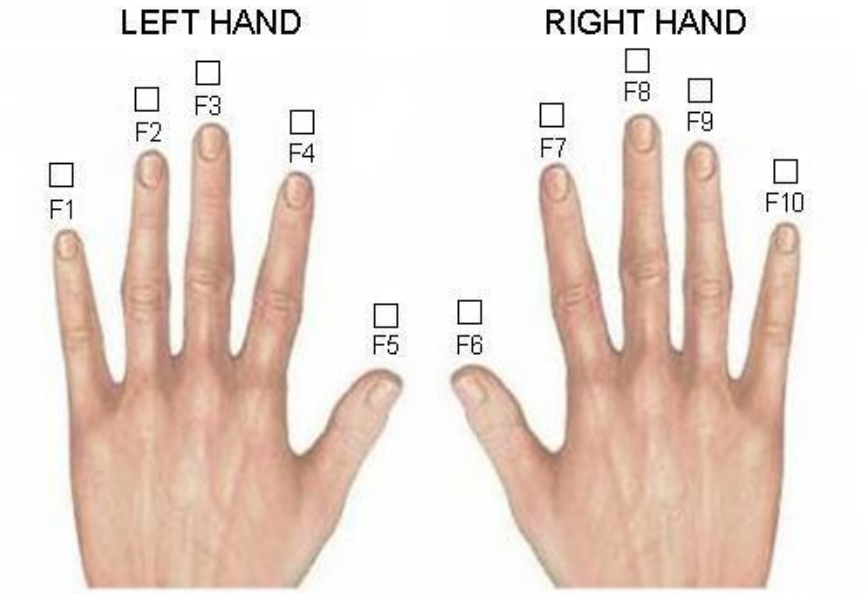
If you answered **NO** to **all** of the questions:

- Collect the toenail samples according to the instructions above
- Place all of the toenail clippings into the plastic bag and seal
- Indicate on the diagram overleaf which nail clippings have been collected
- Put the folded instruction leaflet and the sealed plastic bag containing your nail clippings inside the paper envelope
- Write the date that the nails were clipped on the paper envelope in the space provided
- Send the envelope to the Study Office

Please indicate by ticking the boxes on the diagram below, which toes you have taken clippings from.



If you have not been able to collect toenail clippings, please indicate on the diagram below, which fingers you have taken clippings from.



Please fold up this instruction leaflet. Put the folded leaflet and the plastic bag containing your nail clippings into the paper envelope provided.

DECLARATION OF HELSINKI (SOUTH AFRICA REVISION 1996)

HUMAN EXPERIMENTATION

In 1964, the World Medical Association drew up a code of ethics on human experimentation. This code, known as the Declaration of Helsinki, as amended by the 29th World Medical Assembly, Tokyo, Japan in 1975, the 35th World Medical Assembly, Venice, Italy, in 1983 and the 41st World Medical Assembly, Hong Kong in 1989 and the 48th General Assembly, South Africa in 1996 reads:

It is the mission of the medical doctor to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

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."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic and prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical Progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the fields of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special 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.

Because it is essential that the results of the laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil or ethical responsibilities under the laws of their own country.

1. Basic principles

(1) Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and a thorough knowledge of the scientific literature.

(2) The design and performance of each procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

(3) Biomedical 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 the medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

(4) Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

(5) Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risk in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

(6) The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the trial on the subject's physical and mental integrity and on the personality of the subject.

(7) Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

(8) In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

(9) In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the trial and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the trial and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.

(10) When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

(11) In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent the minor's legal guardian.

(12) The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II Medical Research combined with professional care (Clinical research)

(1) In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

(2) The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic method.

In any medical trial, every patient - including those of a control group, if any - should be assured of the best-proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

(4) The refusal of the patient to participate in a trial must never interfere with the physician-patient relationship.

(5) If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1.2).

(6) The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III Non-therapeutic biomedical research involving human subjects (Non-clinical biomedical research)

(1) In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

(2) The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

(3) The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

(4) In research on man, the interest of science and society should never take precedence over considerations related to the well being of the patient.

APPENDIX 16
REFERENCES

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