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The Graham Roberts Study: a first "Trials within Cohort study" for bladder cancer

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Keywords:	trials within cohorts, bladder cancer, randomised control trial, prospective cohort study

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Abstract

Background: Given the need for more bladder cancer research and the recently observed advantages of introducing the trials within cohort (TwiCs) design, the set-up of the Graham Roberts Study (Roberts Study) will provide valuable infrastructure to answer a wide variety of research questions of a clinical, mechanistic, as well as supportive care nature in the area of bladder cancer.

Methods: Using the TwiCs design, we will recruit patients aged 18 or older who are willing and able to provide signed informed consent and have a diagnosis of an active new or recurrent bladder cancer into this prospective cohort study. All patients have to have a basic understanding of the English language. The following questionnaires will be collected baseline and every 12 months: Functional assessment of chronic illness therapy for bladder cancer (FACT-Bl), the Functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue), the Patient health questionnaire-9 (PHQ-9), the Standardised instrument for a generic health status (EQ-5D-5L), a questionnaire to assess health enhancing physical activity (SQUASH), and the Hertfordshire short questionnaire to assess diet quality.

Discussion: The main outcome of this work will thus be a well-annotated cohort of bladder cancer patients that provides the opportunity to address a wide variety of important research questions. It will also allow the efficient set-up of new randomised controlled trials (RCTs) for bladder cancer patients (e.g. a smoking cessation intervention), whilst making use of the linkage with our existing King's Health Partners' Bladder Cancer Biobank.

Keywords: trials within cohorts, bladder cancer, randomised controlled trial, prospective cohort study

Strengths and Limitations

1. First trials within cohort (TwiCs) study design for bladder cancer.
2. TwiCs design generates a of wide variety of research opportunities with limited risk to patients.
3. The non-interventional nature of this study means patient participation may not benefit patients' bladder cancer prognosis or quality of life.

Background

Bladder cancer is the 7th most common cancer in the UK, with c.10,400 patients diagnosed annually [1]; c. 50% of patients will survive their cancer for 10 years or more after diagnosis. For the majority of patients, the disease remains indolent following initial treatment, and invasive and burdensome surveillance is required to mitigate the high risk of recurrence [2]. However, there is proportionally less research into bladder cancer compared to breast, prostate or kidney cancer [3]. To provide the most efficient and high impact research strategy for bladder cancer patients in the UK, we have established a prospective cohort study of newly diagnosed bladder cancer patients to allow research that can efficiently address clinical, mechanistic, as well as supportive care related questions. The main outcome of this work will thus be a well-annotated cohort of bladder cancer patients that provides the opportunity to address a wide variety of important research questions. It will also allow the efficient set-up of new randomised controlled trials (RCTs) for bladder cancer patients (e.g. a smoking cessation intervention), whilst making use of the linkage with our existing King's Health Partners' Bladder Cancer Biobank.

The design of this bladder cancer cohort study is similar to the Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaLuAtion (UMBRELLA) [4], which is based on the TwiCs

design introduced by Relton et al. at the University of Sheffield in 2010 [5]. It is the first TwiCs design study in the area of bladder cancer. More information about the TwiCs design can be found below.

The use of TwiCs has grown substantially in the last few years, with several new initiatives in the UK. A 2015 systematic review identified 16 studies implementing the TwiCs design, with a total of 18 ongoing or completed trials embedded within these cohorts [6]. Some cohorts focused on a single disease or injury (e.g. hip fracture, breast cancer, colorectal cancer), whilst others had a wider focus (e.g. risk of mental health conditions, risk of falls). Some studies built a cohort around a trial, and then obtained further funds to exploit the cohort for further trials within that cohort. At least six TwiCs studies are ongoing in the UK [7], of which one is the Yorkshire Health Study [8]. The latter is a longitudinal observational regional health study collecting health information on the residents of the Yorkshire and Humberside region in England [8]. The study principally aims to inform National Health Service (NHS) and local authority health-related decision making in Yorkshire, but with additional wider implications from the findings as well.

The main objectives of the Graham Roberts study (Roberts Study) are:

- To create a prospective cohort study of well-characterised bladder cancer patients, which provides the opportunity to conduct a variety of observational studies.
- To create the infrastructure for future RCTs that will allow more efficient recruitment using patient-centred informed consent

Methods/Design

TwiCs design

TwiCs, originally introduced as cohort multiple randomised controlled trial design, was introduced to address the problems associated with existing approaches for trials informing routine clinical practice [5]. The design can be described as follows: Firstly, a large observational cohort of patients

with the condition of interest is recruited and their outcomes regularly measured. Then for each randomised controlled trial (RCT), information from the cohort is used to identify all eligible patients. Some eligible patients are randomly selected and offered the trial intervention. The outcomes of these randomly selected patients are then compared with the outcomes of eligible patients not randomly selected, that is, those receiving usual care. This process can be repeated for further randomised controlled trials [5].

The recruitment and regular follow-up of a large cohort of patients are characteristics of longitudinal observational studies. In the TwiCs design, however, all patients in the cohort consent at the outset to provide data to be used to look at the benefits of treatments for the condition of interest. The capacity for multiple RCTs over time using patients from the same cohort is unique to the TwiCs design. Random selection of some eligible cohort patients, the comparison of their outcomes with the outcomes in eligible patients not randomly selected and the similarity of the patient-centred informed consent approach to real life situations offer solutions to the ethical criticisms of randomised consent designs [5].

The Graham Roberts Study

Patients will be recruited at Guy's and St Thomas' (GSTT) NHS Foundation Trust, London, UK. All patients following their first visit for their active new or recurrent bladder cancer will be eligible. Patients with limited understanding of the English language and patients under the age of 18 years are ineligible. Since Guy's Hospital is a referral centre the Roberts Study will include patients from secondary and tertiary hospitals. Each year, approximately 100 eligible patients visit GSTT for bladder cancer management.

All eligible patients who have already been informed about a (highly likely) bladder cancer at the time of visiting the Urology Centre, will receive detailed written information about the Roberts Study

whilst waiting for their appointment. They will then be scheduled to see a member of the direct clinical care team and a research nurse/assistant 30 minutes prior to their first appointment with the Consultant (urology or oncology). During this research consultation, the research nurse/assistant will explain the study in detail and written informed consent will be obtained from those who agree to participate. At this time, the patients will also be asked to fill out the baseline questionnaire.

For those eligible patients who have not yet been informed about their bladder cancer at the time of visiting the Urology Centre, detailed written information about the Roberts Study will be provided by a research nurse/assistant after they have met with the consultant. If the patients are not ready to discuss this study in further detail, a follow-up call will be made one week later to obtain their consent, if they have agreed to participate.

The Roberts Study will serve as a facility for multiple trials and follows the TwiCs design. In this context, informed consent will be obtained through a staged procedure [9]. Before entering the cohort, all patients give written informed consent for collection and use of their clinical data. Patient-reported outcomes (PROMs) and other relevant questionnaires are collected at baseline and at fixed intervals during follow-up. At this stage, the patients will also be invited to consent for the King's Health Partner's Cancer Biobank – allowing for a link between the Roberts Study and their biospecimen collection. However, consent to the Biobank is not a requirement for participating in the Roberts Study.

In addition, patients may give consent to be randomly allocated to experimental intervention relating to bladder cancer in the (near) future. Only those patients randomly allocated to the intervention arm will be offered the experimental intervention (which they can accept or decline). If they accept, additional written informed consent to undergo the experimental intervention will be obtained. Patients who decline intervention will receive standard of care, which will be unaffected

by the fact they have declined to participate in the randomised element of this study. Patients who are randomly allocated to the control arm will also receive standard of care, and are not informed about their participation in the control arm. This additional consent will be obtained at the time of consent for the cohort study.

Data from all patients may be used for observational studies in the Roberts Study, but only those who provide consent for randomisation are eligible for participation in the RCTs within the Roberts Study. After completion of an RCT within the Roberts Study, all patients – irrespective of participation in the specific study – will receive aggregated results via a newsletter that they can subscribe to at time of initial consent.

Thus, the TwiCs design is based on an "asymmetric informed consent". After recruitment into the Roberts cohort, randomisation of eligible subjects, can be followed by an asymmetric treatment of the two arms. Those selected for the experimental arm provide informed consent for the intervention trial, while the data from the control arm are used based on prior broad permission. Hence, the cohort participants are informed about future research within the cohort.

Patient and Public Engagement

The development of the Graham Roberts Study was informed in collaboration with patient representatives diagnosed and treated at Guy's and St Thomas' NHS Foundation Trust. Prior to development of the study protocol, a focus group was held to discuss the acceptability of the TwiCs study design and the content of the self-administered questionnaire. Patients of similar bladder cancer diagnoses to those that will be consented onto the study were recruited into this focus group. Based on the patient's experiences and preferences, the Graham Roberts Study design was agreed. Results of the study will be disseminated to the patients through annual newsletters and on a study specific website for patients.

Selection and withdrawal of subjects

Patients eligible to participate in this study are those who meet all of the following inclusion criteria:

- Appointment for an active new or recurrent bladder cancer diagnosis at Guy's and St Thomas' NHS Foundation Trust
- Minimum age of 18 years
- Basic understanding of English

Patients must NOT meet any of the following exclusion criteria:

- Younger than 18 years
- Limited understanding of English

Patients will be identified in multi-disciplinary team meetings or in out-patient clinics by the clinical team, in collaboration with the research nurse. Participants have the right to withdraw from the study at any time for any reason. Their routine medical and surgical care will not be affected.

Expected duration of the study

As this study is an observational prospective cohort study, it is difficult to estimate its duration. We aim to recruit a minimum of 400 patients over a period of 5 years, though there is no limit to the number of patients needed for a prospective cohort study. Moreover, over time new research opportunities will develop and potential funding may become available to continue recruitment into the Roberts Study. Patients will be followed up for life through data linkages with Hospital Episode Statistics (HES), the Office for National Statistics (ONS) and electronic patient records.

Study procedures by visit

All potentially eligible patients who already know they have bladder cancer will receive detailed written information about the Roberts Study whilst they are waiting for their appointment. They will be scheduled to see a member of the direct clinical care team and a research nurse/assistant 30

minutes prior to their appointment with the consultant (urology or oncology). During this research consultation, the research nurse/assistant will explain the study in detail, and written informed consent for entering the cohort and potential entry into an intervention arm will be obtained from those who agree to participate. Patients who require more time to consider their consent, will be given this time and will be approached at their next scheduled clinical visit. If at that time they do not want to consent, patients will not be approached again.

For those eligible patients who have not yet been informed about their bladder cancer at the time of visiting the Urology Centre, detailed written information about the Roberts Study will be provided by a research nurse/assistant after they have met with the consultant. If the patients are not ready to discuss this study in further detail, they will be given more time to consider their consent and will be approached again at their next scheduled clinical visit. If at that time they do not want to consent, patients will not be approached again.

Following this consent (baseline), the patients will be given a variety of questionnaires either on paper or digital (tablet). It will take about 30 minutes to fill out the set of questionnaires at the respective time point. Every 12 months thereafter, with a total follow-up of at least 10 years, patients will be asked to fill out the questionnaires again, which may be sent via post/email or can be filled out in clinic during a regular follow-up visit.

If patients agree to also consent for the King's Health Partners Cancer Biobank (which is not a requirement for being in the Roberts Study) at the time of consenting to the Roberts study, they will also agree to:

- donate paraffin processed tumour samples for research objectives
- have paraffin embedded blocks archived for research objectives

In addition, they may agree to donate additional blood, urine and tissue samples for research. The standard operating procedures and ethical considerations for this entire process can be found elsewhere [10] (REC 12/EE/0493).

Data collection

Within the Roberts Study, various clinical data will be prospectively collected including demographics, tumour characteristics, treatment and imaging data. Clinical data will be captured from electronic medical records, referral letters and annual reports for Public Health England.

Socio-demographic data will include sex, date of birth, age at diagnosis, highest level of education, postal code (to estimate the deprivation index), body mass index (BMI) and WHO performance status.

The following tumour characteristics will be collected: TNM stage, grade, tumour diameter, number of tumours, histology and morphological codes and invasiveness.

Treatment characteristics comprise data on type and timing of treatment given (e.g. intravesical instillations, systemic chemotherapy, radical cystectomy, radiotherapy or other treatments). Table 1 shows the pre-, peri- and postoperative data that will be collected for the radical cystectomy patients.

Preoperative	TNM stage, weight, height, BMI, American Society of Anesthesiologists (ASA) score, previous pelvic surgery, radiation or neoadjuvant chemotherapy
Perioperative	Type of surgery, type of lymphadenectomy, type of urinary diversion, blood loss, duration of surgery, accidental organ injury during surgery
Postoperative	Complications (Clavien-Dindo), re-operations and re-admissions within 90 days, length of hospital stay, pT stage, number of

	excised lymph nodes and number of excised and metastatic lymph nodes

Table 1: Data collection for those participants of the Roberts Study undergoing radical cystectomy.

Information on recurrence and survival will be collected annually by means of the data linkages with HES, ONS and electronic patient records. We will also collect patient-reported outcome measures (PROMs) by means of validated questionnaires designed to quantify health-related Quality of Life (QoL) from the patients' perspective. These questionnaires will be given (paper (post) or digital (email or tablet in clinic)) to patients upon entry into the cohort (baseline) and every 12 months thereafter with a total follow-up of at least 10 years. It will take about 30 minutes to fill out the set of questionnaires at each time point.

PROMs will be collected on QoL, fatigue, anxiety and depression, physical activity, dietary habits as well as risk behaviour in terms of known bladder cancer risk factors. Following an assessment of smoking behaviour, alcohol consumption and occupational bladder cancer risk factors, the following validated questionnaires will be used (see Additional File 1):

- **Quality of Life:** Functional assessment of chronic illness therapy for bladder cancer (FACT-Bl [11])
- **Fatigue:** Functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue [12])
- **Depression:** Patient health questionnaire-9 (PHQ-9 [13])
- **Health** : Standardised instrument for use as a measure of health outcome (EQ-5D-5L[14])
- **Physical activity**: Questionnaire to assess health enhancing physical activity (SQUASH [15])
- **Assessment of dietary habits:** Short questionnaire to assess diet quality [16]

Assessment of safety

As this is a prospective cohort study with no specific interventions, adverse events (AEs) are unlikely to take place. Nevertheless, if filling out questionnaire data should ever result in an AE, it will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 and coded. These will be reported to the Data Monitoring Committee.

Sample size

As this is a prospective cohort study, with no specific primary research question, it is not possible to perform sample size calculations. However, it is still important to consider recruitment rates and response rates to the questionnaires. In the Dutch UMBRELLA study, 1,308 out of 1,485 (88%) patients who were invited consented to cohort participation [4]. Of those, 1,138 (87%) gave consent for randomisation to future interventions. Return rates for questionnaires at baseline were 80%, and varied from 67 to 74% during follow-up. Sixty percent of patients chose to fill out the questionnaires online, while 40% opted for paper questionnaires [4].

Given that we see on average about 150 eligible patients per year, we expect to recruit at least 400 patients over a period of five years. However, as described above, if more research and/or funding opportunities come up, we will continue recruitment into the Roberts study.

Direct Access to Source Data and Documents

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each patient in the Roberts Study. Study personnel will enter data from source documents corresponding to a patient's visit into the protocol-specific electronic case report forms (CRFs) in a dedicated, secure data warehouse. Patients will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or Designee), but will be identified by patient ID numbers.

The database will be safeguarded against unauthorised access with established security procedures; nightly backup of the database and related software files will be maintained. It will be backed up by the database administrator in conjunction with any updates or changes to the database. At pre-specified junctures of the protocol (e.g., production of interim and final reports), data for analysis will be locked and cleaned as per established procedures. The data warehouse will be stored on a secured KCL server and will be managed by a dedicated data scientist for the bladder cancer research team who has an honorary contract with GSTT.

If a correction is required to a CRF, the time and date stamps will track the person entering or updating CRF data and create an electronic audit trail. The Chief Investigator is responsible for reviewing all information collected on patients enrolled in this study for completeness and accuracy.

To enable evaluations and/or audits from regulatory authorities, the CI agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g. CRFs and hospital records), all original signed informed consent forms, safety reporting forms, source documents and detailed records of treatment disposition and adequate documentation of relevant correspondence (e.g. letters, meeting minutes, telephone call reports). The records should be retained by the CI according to the International Conference on Harmonisation (ICH) or local regulations; all study documentation must be retained for 10 years after the study ends.

Ethics and Regulatory Approvals

The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP, and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents were approved by the London – Fulham Research Ethics Committee (REC) as part of gaining Health Research Authority (HRA) approval (17/LO/1975).

Quality Assurance

Monitoring of this study will be to ensure compliance with Good Clinical Practice, and scientific integrity will be managed and oversight retained by the Data Monitoring Committee (DMC) led by Prof Dominique Michaud. The committee will receive notification every 6 months of the interim and total accrual. At the discretion of the chair of the DMC, interim analyses may be scheduled as modifications to the protocol. Additional meetings during the study period may occur at the discretion of the Steering Committee.

The study design, analysis and reporting will follow the recent recommendations for good practice in clinical outcomes assessment by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [17].

Data handling

The Chief Investigator and delegates are responsible for daily cohort management. Data quality will be checked periodically. The following guidelines will be strictly adhered to:

- Patient data will be anonymised.
- All anonymised data will be stored on a password protected encrypted computer.
- All study data will be stored in line with the Data Protection Act as defined in the King's Health Partners' Clinical Trials Office Archiving SOP.

The data will be stored as outlined in the data management plan.

Insurance/Indemnity

The co-sponsors King's College London and Guy's and St Thomas' NHS Foundation Trust will provide insurance and indemnity.

Discussion

The Graham Roberts study is the first of its kind and thus the first TwiCs study for bladder cancer. It generates a wide variety of research opportunities with limited risk to patients. Participation in research involves some loss of privacy. We will do our best to make sure that all personal information gathered for this study is kept private. As this is a non-interventional prospective cohort study, participation may not have a beneficial effect on patients' bladder cancer prognosis or quality-of-life compared to usual care.

The questionnaires to be used are quite detailed and, for the most part, concerns day-to-day activities such as quality and duration of sleep, diet and exercise. The questionnaire does pose some more personal and intrusive questions however, including questions related to symptoms of depression. These questions can be omitted if the participant does not feel comfortable answering them. There is a risk that some participants may be upset by having these questions posed to them. Some participants may prefer to complete the questionnaire themselves, whereas others may prefer to do so with a research assistant. Participants will be fully informed about these potential harms and enabled to make an informed decision regarding participation. We consider that the potential minor harms are outweighed by the potential benefits of the research.

Future research using the data in this study could lead to medical and scientific products, discoveries, as well as interventions that improve the prevention, diagnosis and treatment of

bladder cancer. A benefit for the patients is also the possibility to be part of future RCTs by providing consent for being part of the intervention arm.

Trial Status

Protocol Version and Number: Version 2, January 2018

Date of commencement of recruitment: 22nd February 2018

Projected date of recruitment completion: 28th October 2022

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Additional Files

Additional File 1 – Graham Roberts Study Questionnaire (doc).
The questionnaire given to patients who have consented to the Graham Roberts Study.

List of abbreviations

AE	Adverse events
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CI	Chief Investigator
CRF	Case Research Form
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
EQ-5D-5L	Standardised instrument for use as a measure of health outcome
FACT-Bl	Functional assessment of chronic illness therapy for bladder cancer
FACIT	Functional assessment of chronic illness therapy - fatigue
GCP	Good Clinical Practice
GSTT	Guy's and St Thomas'
HES	Hospital Episode Statistics
HRA	Health Research Authority
ICH	International Conference on Harmonisation
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KCL	King's College London
NHS	National Health Services
ONS	Office National Statistics
PHQ-9	Patient health questionnaire-9
PI	Principle Investigator
PROMS	Patient-reported outcomes
QoL	Quality of Life
RCT	Randomise Clinical Trial
REC	Research Ethics Committee
SOP	Standard Operating Procedures
SQUASH	Questionnaire to assess health enhancing physical activity
TwiCs	Trials within Cohorts
UK	United Kingdom
WHO	World Health Organisation

Declarations

Ethics approval and consent to participate

The Fulham Research Ethics Committee approved the Graham Roberts Study on 22/02/2018 (Reference number: 17/LO/1975).

Consent for publication

Not applicable.

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MVH, FC, HW, CR, CM, and AS designed the study with input from their clinical colleagues (SC, SH, SR, DE, DJ, RB, SA, KC, SK) and the biobank coordinator (CG). All authors read and approved the final manuscript.

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The Graham Roberts Study Protocol: a first "Trials within Cohort study" for bladder cancer

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Abstract

Introduction: Given the need for more bladder cancer research and the recently observed advantages of introducing the trials within cohort (TwiCs) design, the set-up of the Graham Roberts Study (Roberts Study) will provide valuable infrastructure to answer a wide variety of research questions of a clinical, mechanistic, as well as supportive care nature in the area of bladder cancer.

Methods: Using the TwiCs design, we will recruit patients aged 18 or older who are willing and able to provide signed informed consent and have a diagnosis of an active new or recurrent bladder cancer into this prospective cohort study. All patients have to have a basic understanding of the English language. The following questionnaires will be collected baseline and every 12 months: Functional assessment of chronic illness therapy for bladder cancer (FACT-Bl), the Functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue), the Patient health questionnaire-9 (PHQ-9), the Standardised instrument for a generic health status (EQ-5D-5L), a questionnaire to assess health enhancing physical activity (SQUASH), and the Hertfordshire short questionnaire to assess diet quality.

Ethics and Dissemination: Due to the nature of this study, we obtained full ethical clearance from the London - Fulham Research Ethics Committee (17/LO1975). All participants must provide full informed consent before recruitment onto the study. The results of this study will be published in peer-reviewed journals and data collected as part of the study will be made available to potential collaborators on an application basis.

Keywords: trials within cohorts, bladder cancer, randomised controlled trial, prospective cohort study

Strengths and Limitations

1. First trials within cohort (TwiCs) study design for bladder cancer.
2. TwiCs design generates a of wide variety of research opportunities with limited risk to patients.
3. The non-interventional nature of this study means patient participation may not benefit patients' bladder cancer prognosis or quality of life.

Background

Bladder cancer is the 7th most common cancer in the UK, with c.10,400 patients diagnosed annually (1); c. 50% of patients will survive their cancer for 10 years or more after diagnosis. For the majority of patients, the disease remains indolent following initial treatment, and invasive and burdensome surveillance is required to mitigate the high risk of recurrence (2). However, there is proportionally less research into bladder cancer compared to breast, prostate or kidney cancer (3). To provide the most efficient and high impact research strategy for bladder cancer patients in the UK, we have established a prospective cohort study of newly diagnosed bladder cancer patients to allow research that can efficiently address clinical, mechanistic, as well as supportive care related questions.

The design of this bladder cancer cohort study is similar to the Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaLuAtion (UMBRELLA) (4), which is based on the TwiCs design introduced by Relton et al. at the University of Sheffield in 2010 (5). It is the first TwiCs design study in the area of bladder cancer.

The use of TwiCs has grown substantially in the last few years, with several new initiatives in the UK. TwiCs, originally introduced as cohort multiple randomised controlled trial design, was introduced to address the problems associated with existing approaches for trials informing routine clinical

practice(5). Such shortcomings relate to recruitment, ethics, patient preferences and treatment comparisons. At least six TwiCs studies are currently ongoing in the UK (6).

The Roberts Study will serve as a facility for multiple trials and follows the TwiCs design.

The main objectives of the Graham Roberts study (Roberts Study) are:

- To create a prospective cohort study of well-characterised bladder cancer patients, which provides the opportunity to conduct a variety of observational studies.
- To create the infrastructure for future RCTs that will allow more efficient recruitment using patient-centred informed consent

Methods/Design

TwiCs design

The TwiCs design can be described as follows: Firstly, a large observational cohort of patients with the condition of interest is recruited and their outcomes regularly measured. Then for each randomised controlled trial (RCT), information from the cohort is used to identify all eligible patients. Some eligible patients are randomly selected and offered the trial intervention. The outcomes of these randomly selected patients are then compared with the outcomes of eligible patients not randomly selected, that is, those receiving usual care. This process can be repeated for further randomised controlled trials (5).

The recruitment and regular follow-up of a large cohort of patients are characteristics of longitudinal observational studies. In the TwiCs design, however, all patients in the cohort consent at the outset to provide data to be used to look at the benefits of treatments for the condition of interest. The capacity for multiple RCTs over time using patients from the same cohort is unique to the TwiCs design. Random selection of some eligible cohort patients, the comparison of their outcomes with

the outcomes in eligible patients not randomly selected and the similarity of the patient-centred informed consent approach to real life situations offer solutions to the ethical criticisms of randomised consent designs (5).

The Graham Roberts Study

Patients will be recruited at Guy's and St Thomas' (GSTT) NHS Foundation Trust, London, UK. All patients will be eligible for the study following their first visit for a new or recurrent bladder cancer diagnosis. Patients with limited understanding of the English language and patients under the age of 18 years are ineligible. Since Guy's and St Thomas NHS Foundation Trust is a referral centre, the Roberts Study will include patients from various secondary and tertiary hospitals located across the United Kingdom. Each year, approximately 100 eligible patients visit the Urology Centre of GSTT for bladder cancer management.

All eligible patients who have already undergone diagnostic investigations and been informed about a (highly likely) bladder cancer will receive detailed written information about the Roberts Study whilst attending the Urology Centre for their initial appointment. They will be scheduled to see a member of the direct clinical care team and a research nurse/assistant 30 minutes prior to their first appointment with the Consultant (urology or oncology). During this research consultation, the research nurse/assistant will explain the study in detail and written informed consent will be obtained from those who agree to participate. Such consent will be gained to allow:

- Participation in the Graham Robert's Study cohort and longitudinal study;
- The participant to be approached to participate in the intervention arm of any future randomised control trial;
- The participant to be randomised to the control arm of any future randomised control trial without knowledge of this status.

- Collection and storage of participants biological samples, including blood, urine and tissue, within the KHP Bladder Cancer Biobank;
- Linkage and use of participants routinely collected clinical data as recorded in electronic patient records.

At the time of full informed consent, the patients will also be provided with the study baseline questionnaire and asked to complete this at a convenient time.

For those eligible patients who have not yet been informed about their bladder cancer diagnosis at the time of visiting the Urology Centre, detailed written information about the Roberts Study will be provided by a research nurse/assistant after they have met with the consultant. If the patients are not ready to discuss this study in further detail at this point, a follow-up call will be made one week later to obtain their consent, if they have agreed to participate. Full written informed consent is subsequently obtained at the patients next clinical appointment.

Data from all patients may be used for observational studies in the Roberts Study, but only those who provide consent for randomisation are eligible for participation in the RCTs within the Roberts Study.

Thus, the TwiCs design is based on an “asymmetric informed consent”. After recruitment into the Roberts cohort, randomisation of eligible subjects, can be followed by an asymmetric treatment of the two arms; those selected for the experimental arm provide informed consent for the intervention trial, while the data from the control arm are used based on prior broad permission. Hence, the cohort participants are informed about future research within the cohort.

Selection and withdrawal of subjects

Patients eligible to participate in this study are those who meet all of the following inclusion criteria:

- Appointment for a new or recurrent diagnosis of bladder cancer at Guy's and St Thomas' NHS Foundation Trust
- Minimum age of 18 years
- Basic understanding of English

Patients will be identified in multi-disciplinary team meetings or in out-patient clinics by the clinical team, in collaboration with the research nurse. Participants have the right to withdraw from the study at any time for any reason. Their routine medical and surgical care will not be affected.

Expected duration of the study and sample size

As this study is an observational prospective cohort study, it is difficult to estimate its duration. We aim to recruit a minimum of 400 patients over a period of 5 years, though there is no limit to the number of patients needed for a prospective cohort study. Moreover, over time new research opportunities will develop and potential funding may become available to continue recruitment into the Roberts Study. Patients will be followed up for life through data linkages with Hospital Episode Statistics (HES), the Office for National Statistics (ONS) and electronic patient records.

As this is a prospective cohort study, with no specific primary research question, it is not possible to perform sample size calculations. However, it is still important to consider recruitment rates and response rates to the questionnaires.

At the point of submission of this protocol (April 2019), 72 bladder cancer patients had provided full written informed consent for the Graham Robert's Study. Of these 72 patients, 64 had completed and returned their baseline questionnaire. At current rates of consent, the authors would expect baseline recruitment of 400 bladder cancer patients to be complete by 31st December 2022.

Data collection

Within the Roberts Study, various clinical data will be prospectively collected including demographics, tumour characteristics, treatment and CT and MRI imaging data. Clinical data will be captured from electronic medical records, referral letters and annual reports for Public Health England.

Socio-demographic data will include sex, date of birth, age at diagnosis, highest level of education, postal code (to estimate the deprivation index), body mass index (BMI) and WHO performance status.

The following tumour characteristics will be collected: TNM stage, grade, tumour diameter, number of tumours, histology and morphological codes and invasiveness.

Treatment characteristics comprise data on type and timing of treatment given (e.g. intravesical instillations, systemic chemotherapy, radical cystectomy, radiotherapy or other treatments). Additional detailed data, as reported in surgical notes, will be available for those bladder cancer patients who undergo radical cystectomy. Table 1 illustrates the pre-, peri- and postoperative variables which will be collected for this patient subset.

Table 1: Data collection for those participants of the Roberts Study undergoing radical cystectomy.Preoperative	TNM stage, weight, height, BMI, American Society of Anesthesiologists (ASA) score, previous pelvic surgery, radiation or neoadjuvant chemotherapy
Perioperative	Type of surgery, type of lymphadenectomy, type of urinary diversion, blood loss, duration of surgery, accidental organ injury during surgery
Postoperative	Complications (Clavien-Dindo), re-operations and re-admissions within 90 days, length of hospital stay, pT stage, number of excised lymph nodes and number of excised and metastatic lymph nodes

Information on disease progression, recurrence and survival will be collected annually by means of the data linkages with HES, ONS and electronic patient records. We will also collect patient-reported outcome measures (PROMs) by means of validated questionnaires designed to quantify health-related Quality of Life (QoL) from the patients' perspective. These questionnaires will be given (paper (post) or digital (email or tablet in clinic)) to patients upon entry into the cohort (baseline) and every 12 months thereafter with a total follow-up of at least 10 years. It will take about 30 minutes to fill out the set of questionnaires at each time point.

PROMs will be collected on QoL, fatigue, anxiety and depression, physical activity, dietary habits as well as risk behaviour in terms of known bladder cancer risk factors. Following an assessment of smoking behaviour, alcohol consumption and occupational bladder cancer risk factors, the following validated questionnaires will be used (see Additional File 1):

- **Quality of Life:** Functional assessment of chronic illness therapy for bladder cancer (FACT-Bl (7))
- **Fatigue:** Functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue (8))
- **Depression:** Patient health questionnaire-9 (PHQ-9 (9))
- **Health** : Standardised instrument for use as a measure of health outcome (EQ-5D-5L(10))
- **Physical activity**: Questionnaire to assess health enhancing physical activity (SQUASH (11))
- **Assessment of dietary habits:** Short questionnaire to assess diet quality (12)

Assessment of safety

As this is a prospective cohort study with no specific interventions, adverse events (AEs) are unlikely to take place. Nevertheless, if filling out questionnaire data should ever result in an AE, it will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 and coded. These will be reported to the Data Monitoring Committee.

Given that we see on average about 100 eligible patients per year, we expect to recruit at least 400 patients over a period of five years. However, as described above, if more research and/or funding opportunities come up, we will continue recruitment into the Roberts study.

Patient and Public Engagement

The development of the Graham Roberts Study was informed in collaboration with patient representatives diagnosed and treated at Guy's and St Thomas' NHS Foundation Trust. Prior to development of the study protocol, a focus group was held to discuss the acceptability of the TwiCs study design and the content of the self-administered questionnaire. Patients of similar bladder cancer diagnoses to those that will be consented onto the study were recruited into this focus group. Based on the patient's experiences and preferences, the Graham Roberts Study design was agreed. Results of the study will be disseminated to the patients through annual newsletters and on a study specific website for patients.

Direct Access to Source Data and Documents

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each patient in the Roberts Study. Study personnel will enter data from source documents corresponding to a patient's visit into the protocol-specific electronic case report forms (CRFs) in a dedicated, secure data warehouse. Patients will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or Designee), but will be identified by patient ID numbers.

The database will be safeguarded against unauthorised access with established security procedures; nightly backup of the database and related software files will be maintained. At pre-specified junctures of the protocol (e.g., production of interim and final reports), data for analysis will be locked and cleaned as per established procedures.

If a correction is required to a CRF, the time and date stamps will track the person entering or updating CRF data and create an electronic audit trail. The Chief Investigator is responsible for reviewing all information collected on patients enrolled in this study for completeness and accuracy.

To enable evaluations and/or audits from regulatory authorities, the CI agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g. CRFs and hospital records), all original signed informed consent forms, safety reporting forms, source documents and detailed records of treatment disposition and adequate documentation of relevant correspondence (e.g. letters, meeting minutes, telephone call reports). The records should be retained by the CI according to the International Conference on Harmonisation (ICH) or local regulations; all study documentation must be retained for 10 years after the study ends.

Quality Assurance

Monitoring of this study will be to ensure compliance with Good Clinical Practice, and scientific integrity will be managed and oversight retained by the Data Monitoring Committee (DMC) led by Prof Dominique Michaud. The committee will receive notification every 6 months of the interim and total accrual. At the discretion of the chair of the DMC, interim analyses may be scheduled as modifications to the protocol. Additional meetings during the study period may occur at the discretion of the Steering Committee.

The study design, analysis and reporting will follow the recent recommendations for good practice in clinical outcomes assessment by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (13).

Data handling

The Chief Investigator and delegates are responsible for daily cohort management. Data quality will be checked periodically. The following guidelines will be strictly adhered to:

- Patient data will be anonymised.
- All anonymised data will be stored on a password protected encrypted computer.
- All study data will be stored in line with the Data Protection Act as defined in the King's Health Partners' Clinical Trials Office Archiving SOP.

The data will be stored as outlined in the data management plan.

Insurance/Indemnity

The co-sponsors King's College London and Guy's and St Thomas' NHS Foundation Trust will provide insurance and indemnity.

Discussion

The Graham Roberts study is the first of its kind and thus the first TwiCs study for bladder cancer. It generates a wide variety of research opportunities with limited risk to patients. Participation in research involves some loss of privacy. We will do our best to make sure that all personal information gathered for this study is kept private. As this is a non-interventional prospective cohort study, participation may not have a beneficial effect on patients' bladder cancer prognosis or quality-of-life compared to usual care.

The questionnaires to be used are quite detailed and, for the most part, concerns day-to-day activities such as quality and duration of sleep, diet and exercise. The questionnaire does pose some more personal and intrusive questions however, including questions related to symptoms of depression. These questions can be omitted if the participant does not feel comfortable answering them. There is a risk that some participants may be upset by having these questions posed to them.

Some participants may prefer to complete the questionnaire themselves, whereas others may prefer to do so with a research assistant. Participants will be fully informed about these potential harms and enabled to make an informed decision regarding participation. We consider that the potential minor harms are outweighed by the potential benefits of the research.

Future research using the data in this study could lead to medical and scientific products, discoveries, as well as interventions that improve the prevention, diagnosis and treatment of bladder cancer. A benefit for the patients is also the possibility to be part of future RCTs by providing consent for being part of the intervention arm.

Trial Status

Protocol Version and Number: Version 2, January 2018

Date of commencement of recruitment: 22nd February 2018

Projected date of recruitment completion: 28th October 2022

Ethics and Dissemination

The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP, and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments. This protocol and related documents were approved by the London – Fulham Research Ethics Committee (REC) as part of gaining Health Research Authority (HRA) approval (17/LO/1975).

After completion of an RCT within the Roberts Study, all patients – irrespective of participation in the specific study – will receive aggregated results via a newsletter that they can subscribe to at time of

initial consent. All results associated with this study will be published in journals as peer-reviewed articles.

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Additional Files

Additional File 1 – Graham Roberts Study Questionnaire (doc).
The questionnaire given to patients who have consented to the Graham Roberts Study.

List of abbreviations

AE	Adverse events
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CI	Chief Investigator
CRF	Case Research Form
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
EQ-5D-5L	Standardised instrument for use as a measure of health outcome
FACT-Bl	Functional assessment of chronic illness therapy for bladder cancer
FACIT	Functional assessment of chronic illness therapy - fatigue
GCP	Good Clinical Practice
GSTT	Guy's and St Thomas'
HES	Hospital Episode Statistics
HRA	Health Research Authority
ICH	International Conference on Harmonisation
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KCL	King's College London
NHS	National Health Services
ONS	Office National Statistics
PHQ-9	Patient health questionnaire-9
PI	Principle Investigator
PROMS	Patient-reported outcomes
QoL	Quality of Life
RCT	Randomise Clinical Trial
REC	Research Ethics Committee
SOP	Standard Operating Procedures
SQUASH	Questionnaire to assess health enhancing physical activity
TwiCs	Trials within Cohorts
UK	United Kingdom
WHO	World Health Organisation

Declarations

Ethics approval and consent to participate

The Fulham Research Ethics Committee approved the Graham Roberts Study on 22/02/2018 (Reference number: 17/LO/1975).

Consent for publication

Not applicable.

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MVH, FC, HW, CR, CM, and AS designed the study with input from their clinical colleagues (SC, SH, SR, DE, DJ, RB, SA, KC, SK) and the biobank coordinator (CG). All authors read and approved the final manuscript.

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Graham Roberts Study (Roberts Study)

Patient Questionnaire

Through the Roberts Study, we are learning about why some bladder cancers respond better to treatment than others. This will help us to develop new and better ways of predicting recurrence and progression of bladder cancer in the future, as well as new interventions that can improve quality and quantity of life. Your participation is a critical contribution toward this goal.

This questionnaire is confidential. We will be taking every step to ensure that your answers to the interview questions are stored securely and are not shared with anyone outside the study team.

If you need any help with any of the questions, please feel free to ask the study team.

Participant number: _____

Date of Birth: _____

Date of Questionnaire: _____

Is this the first time you have filled in this questionnaire? Yes/No

*If this is not the first time you have filled in the questionnaire, please skip **section 1 and 2** and proceed immediately to **section 3** below.*

Section 1 – Personal details and medical history

1. **How would you describe your race / ethnic background?**

   White/Caucasian ☐ Black/Afro-Caribbean ☐ Asian ☐ Other ☐

   If other, please specify.....

2. **What is your current marital status?**

   Married ☐ Divorced/Separated ☐ Widowed ☐ Never married ☐

3. **What is your current living arrangement?**

   Alone ☐ With partner ☐ With other family ☐

   Assisted Living ☐ Nursing Home ☐ Other ☐

4. **What is your current work status?**

   Full-time ☐ Part-time ☐ Retired ☐

   Disabled ☐ Unemployed ☐

5. **What is your highest level of education?**

   Primary school ☐ Higher education (e.g. University) ☐

   Secondary school ☐ Other ☐

For the following questions please circle or tick the appropriate answer:

6. **Have you ever had any type of cancer (except for non-melanoma skin cancer)?**

   YES NO
   If you answered yes, please specify: _____

7. **Were any of your immediate blood relatives, that is, your mother, or father, or sister(s), or brother(s), or son(s), or daughter(s), ever diagnosed as having any type of cancer?**
   - □ Yes
   - □ No – please continue to question 8
   - □ I prefer not to answer
   - □ I don't know

   Who was/were diagnosed as having cancer, that is, what was his or her relationship to you?
   - □ Mother
   - □ Father
   - □ Brother(s)
   - □ Sister(s)
   - □ Son(s)
   - □ Daughter(s)
   - □ I prefer not to answer
   - □ I don't know

   You indicated that at least one of your immediate blood relatives was diagnosed with cancer. Was he/she, or at least one of them (if more than one), diagnosed with **bladder cancer**?
   - □ Yes
   - □ No
   - □ I prefer not to answer
   - □ I don't know

8. **Did you ever have a bladder infection with at least one of the following symptoms: frequent urination or pain or burning when urinating?**
   - □ Yes
   - □ No
   - □ I prefer not to answer
   - □ I don't know

   How many times did you have this kind of infection? Would you say:
   - □ 1 or 2 times,
   - □ 3 or 5 times,
   - □ 6 or 10 times,
   - □ 11 or more times?
   - □ I prefer not to answer
   - □ I don't know

   How old were you when you first had this type of infection?
   When I was _____ years old
   - □ I prefer not to answer
   - □ I don't know

9. Did you ever have a kidney infection diagnosed by a physician?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

How many times did you have this kind of infection? Would you say:

- □ 1 or 2 times,
- □ 3 or 5 times,
- □ 6 or 10 times,
- □ 11 or more times?
- □ I prefer not to answer
- □ I don't know

10. Before 1 year ago, did you ever have renal or nephritic colic, or kidney or renal stones?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

11. Before 1 year ago, did you ever have urinary bladder stones?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

12. Before 1 year ago, did you ever have a growth removed from your urinary bladder?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

13. Did you ever have any of the following symptoms when urinating: difficulty starting, difficulty stopping or increased frequency during the night?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

14. If you are a man, please answer the following question: Did your doctor ever tell you that you had an enlarged prostate?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

[Women only] The next group of questions are about your reproductive history. Firstly, how old were you when you had your first menstrual period?

[ ] years old

- □ I prefer not to answer
- □ I don't know

Have you had at least one menstrual period in the past 12 months?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

Are you pregnant or breastfeeding?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

Have you had surgery to remove your uterus (hysterectomy)?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

Have you had any of your ovaries surgically removed (oophorectomy)?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

How many of your ovaries were removed?

- □ One
- □ Both
- □ I prefer not to answer
- □ I don't know

Have you ever taken birth control pills?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

At what age did you first start taking birth control pills?

_____ year old

- □ I prefer not to answer
- □ I don't know

How long did you take birth control pills?

_____ years _____ months

- □ I prefer not to answer
- □ I don't know

How many times have you been pregnant?

- □ Never
- □ _____ times
- □ I prefer not to answer
- □ I don't know

How many of your pregnancies ended in a live birth?

_____

- □ I prefer not to answer
- □ I don't know

Section 2 – History of tobacco consumption

Please tick the most appropriate answer:

1. **During your entire lifetime, have you smoked a total of 100 cigarettes or more, which is 5 or more packs?**
   - □ Yes
   - □ No
   - □ I prefer not to answer
   - □ I don't know

2. **Did you ever smoke cigarettes regularly, that is, at least one per day for six months or longer?**
   - □ Yes
   - □ No
   - □ I prefer not to answer
   - □ I don't know

3. **Think about all the years that you smoked cigarettes, how many cigarettes per day did you usually smoke?**
   - □ Less than one
   - □ _____
     [please enter a number if it is more than 1, but less than 95]
   - □ More than 95
   - □ I prefer not to answer
   - □ I don't know

4. **How old were you when you first started smoking at least one cigarette per day?**
   years old
   - □ I prefer not to answer
   - □ I don't know

5. **How old were you when you last smoked cigarettes?**
   _____ years old
   - □ I still smoke
   - □ I refuse to answer
   - □ I don't know

6. **When you smoked cigarettes, would you say that you usually inhaled only into your mouth, into your mouth and throat or into your chest?**
   - □ Mouth only
   - □ Mouth and throat
   - □ Chest
   - □ I do not inhale
   - □ Cannot say, but not deeply into the chest
   - □ I prefer not to answer
   - □ I don't know

7. **Have you ever smoked at least one cigar per week for six months or longer?**
   - □ Yes
   - □ No
   - □ I prefer not to answer
   - □ I don't know

8. How old were you when you first started smoking at least one cigar per week?

_____ years old

□ I refuse to answer

□ I don't know

9. How old were you when you last smoked cigars?

_____ years old

□ I still smoke cigars

□ I refuse to answer

□ I don't know

10. For how many years altogether have you smoked/did you smoke cigars? Please do not include any periods during which you may have quit.

_____ years _____ months

□ I don't know

□ I prefer not to answer

11. Thinking about all the years that you smoked cigars, how many cigars did you usually smoke in a week?

□ Less than one

□ _____

[please enter a number if it is more than 1 but less than 95]

□ More than 95

□ I refuse to answer

□ I don't know

12. Have you ever smoked at least one pipe of tobacco per week for six months or longer?

□ Yes

□ No

□ I prefer not to answer

□ I don't know

13. How old were you when you first started smoking at least one pipe of tobacco per week?

_____ years old

□ I refuse to answer

□ I don't know

14. How old were you when you last smoked a pipe?

_____ years old

□ I still smoke a pipe

□ I refuse to answer

□ I don't know

Section 3 – Current medical conditions and medications

1. Have you been diagnosed with any of the following medical conditions?'

(a) High blood pressure	YES	NO
(b) Diabetes mellitus	YES	NO
(c) High cholesterol	YES	NO
(d) Myocardial infarction (heart attack)	YES	NO
(e) Angina pectoris	YES	NO
(f) Atrial fibrillation	YES	NO
(g) Congestive heart failure	YES	NO

2. Have you regularly taken any of these medications *in the last two years*?

(a) Non-steroidal anti-inflammatory drugs (NSAIDs)

(i) Aspirin	YES	NO
(ii) Ibuprofen (e.g. Advil, Nurofen, Nuprin, Medipren)	YES	NO
(iii) Other: _____	YES	NO

(b) "Statin" cholesterol-lowering drugs

(i) Lovastatin (e.g. Mevacor, Altocor)	YES	NO
(ii) Simvastatin (e.g. Zocor)	YES	NO
(iii) Pravastatin (e.g. Pravachol, Pravigard)	YES	NO
(iv) Atorvastatin (e.g. Lipitor)	YES	NO
(v) Other: _____	YES	NO

(c) Beta blocker drugs

(i) Metoprolol (e.g. Lopressor, Toprol)	YES	NO
(ii) Atenolol (e.g. Tenormin)	YES	NO
(iii) Nadolol (e.g. Corgard)	YES	NO
(iv) Other: _____	YES	NO

(d) Antidepressants: Selective serotonin reuptake inhibitors (SSRIs)

(i) Citalopram (e.g. Celexa)	YES	NO
(ii) Escitalopram (e.g. Lexapro)	YES	NO
(iii) Fluoxetine (e.g. Prozac)	YES	NO
(iv) Paroxetine (e.g. Paxil)	YES	NO
(v) Sertraline (e.g. Zoloft)	YES	NO
(vi) Fluvoxamine (e.g. Luvox)	YES	NO
(vii) Other: _____	YES	NO

(e) Other antidepressants

(i) Amitriptyline (e.g. Elavil, Endep)	YES	NO
(ii) Imipramine (e.g. Tofranil)	YES	NO
(iii) Nortriptyline (e.g. Pamelor)	YES	NO
(iv) Other: _____	YES	NO

(f) Sleeping tablets

(i) Diazepam (e.g. Valium)	YES	NO
(ii) Alprazolam (e.g. Xanax)	YES	NO
(iii) Lorazepam (e.g. Ativan)	YES	NO
(iv) Chlordiazepoxide (e.g. Librium)	YES	NO
(v) Other: _____	YES	NO

(g) Diabetes medications

(i) Insulin	YES	NO
(ii) Metformin	YES	NO
(iii) Rosiglitazone (e.g. Avandia)	YES	NO
(iv) Pioglitazone (e.g. Actos)	YES	NO
(v) Other: _____	YES	NO

(h) Are you on any other long-term medication? _____

Section 4 – Current smoking behaviour, alcohol consumption and other environmental/occupational exposures

Please circle the most appropriate answer:

1. **Do you currently smoke cigarettes, a pipe or cigars? If you answered YES, how many cigarettes, pipe refills or cigars do you smoke per day?**

	Cigarettes		Pipe		Cigars	
Currently smoke?	YES	NO	YES	NO	YES	NO
If yes, how many per day?	1-4 5-14 15-24 25-34 35-44 45 or more		1-4 5-10 10 or more		1-4 5-10 10 or more	

2. **In a typical week over the past three months, on how many days did you consume an alcoholic drink of any type?**

No days *1 day per week* *2 days per week* *3 days per week*

4 days per week *5 days per week* *6 days per week* *7 days per week*

3. **In a typical month, what is the largest number of drinks of beer, wine and / or spirits you have in one day?**

None *1-2 drinks per day* *3-5 drinks per day*

6-9 drinks per day *10-14 drinks per day* *15 or more drinks per day*

4. **On a typical day, what is the total number of alcoholic and non-alcoholic drinks combined you have in one day?**

1-*2 pints per day* *3-5 pints per day*

6-9 pints per day *10-14 pints per day* *15 or more pints per day*

5. **On a typical day, how many cups of coffee do you drink in one day?**

None 1-*2 cups per day* *3-5 cups per day*

6-9 cups per day *10 or more cups per day*

6. **Have you ever worked in the production of rubber or aluminium or were you exposed to aromatic amines (eg. printing or dye industry) for five years or more?** YES NO

7. **Do you get your drinking water from a private well?** YES NO

Section 5 – Quality of Life (FACT-BI)

Below is a list of statements that other people have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BL1	I have trouble controlling my urine	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
C5	I have diarrhoea	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BL3	It burns when I urinate	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BL5	(For men only) I am able to have and maintain an erection	0	1	2	3	4
Q2	Do you have an ostomy appliance? No___ Yes___ If yes, answer the following two items: ↓					
C8	I am embarrassed by my ostomy appliance	0	1	2	3	4
C9	Caring for my ostomy appliance is difficult	0	1	2	3	4

Section 6 – Fatigue (FACIT - Fatigue)

Below is a list of statements that other people have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Section 7 – Anxiety and Depression (PHQ-9)

Over the past 2 weeks, how often have you been bothered by any of the following problems?	Not At all	Several Days	More Than Half the Days	Nearly Every Day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3
3. Trouble falling asleep, staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself - or that you're a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or, the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
Column Totals	_____	+ _____	+ _____	
Add Totals Together	_____			

10. If you checked off any problems, how difficult have those problems made it for you to Do your work, take care of things at home, or get along with other people?

☐ Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult

Section 8 – Health Questionnaire (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

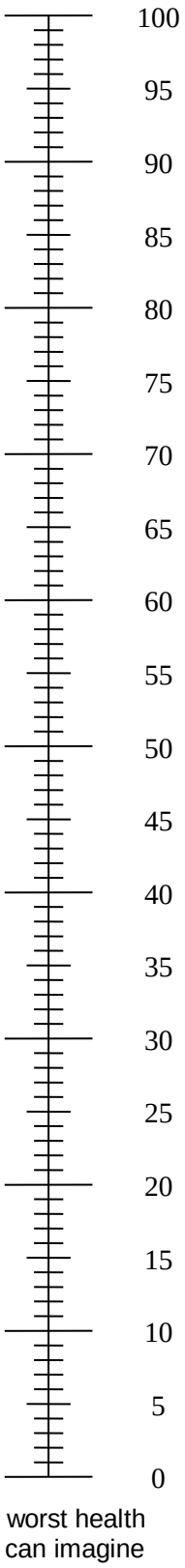
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Section 9 – Physical activity

Think about an average week in the past months. Please indicate **how many days per week** you performed the following activities, how much time on average you were engaged in this, and (if applicable) how strenuous this activity was for you?

	Days per week	Average time per day	Effort (circle please)
Walking	days	hours minutes	slow/moderate/fast
Bicycling	days	hours minutes	slow/moderate/fast
Other physical activity (e.g. swimming, gym, gardening)	days	hours minutes	slow/moderate/fast

If you wear a pedometer on a regular basis, on average how many steps a day to you take?

<2500 steps *2500-4999 steps* *5000-9999 steps*

10000 or more steps *N/A – do not use*

Section 10 – Diet (Hertfordshire Short Questionnaire)

The section below asks you about how often over the past 3 months you have eaten particular foods.

	FOOD AND AMOUNTS	AVERAGE USE IN PAST 3 MONTHS									
		Never	Less than once/month	1-3 per month	Once a week	2-4 pe week	5-6 week	Once a day	2-3 per day	4-5 pe day	6+ per day
1	White bread (one slice)										
2	Brown and wholemeal bread (one slice)										
3	Biscuits eg digestive (one)										
4	Apples (one fruit)										
5	Bananas (one fruit)										
6	Melon, pineapple, kiwi and other tropical fruits (medium serving)										
7	Green salad eg lettuce, cucumber, celery										
8	Garlic – raw and cooked dishes										
9	Marrow and courgettes										
10	Pepper – cooked and fresh										
11	Yogurt (125g pot)										
12	Egg as boiled, fried, scrambled, etc (one egg)										
13	White fish eg cod, haddock, plaice, sole (not in batter/crumbs)										
14	Oily fish, eg mackerel, tuna, salmon										
15	Bacon and gammon										
16	Meat pies, eg pork pie, pasties, steak & kidney, sausage rolls										
17	Boiled, mashed and jacket potatoes (one egg size potato)										
18	Chips										
19	Pasta eg spaghetti, macaroni										
Which is the main spreading fat you have used for example on bread or vegetables?											
20	Spreading fat (teaspoon) _____										

ADDITIONAL DIETARY QUESTIONS

Q21 Which types of milk have you used regularly in drinks and added to breakfast cereals over the past three months? Circle all that apply.

1. Whole pasteurised
2. Semi-skimmed pasteurised (include 1% milks)
3. Skimmed pasteurised
4. Whole UHT
5. Semi-skimmed UHT
6. Skimmed UHT
7. Other: _____ (please specify)
8. None (go to Q23)

Of the above, which are the three types of milk that you drink most commonly?

Number ____ (Milk A)

Number ____ (Milk B)

Number ____ (Milk C)

Q22 On average over the past three months how much of the above have you consumed per day?

Milk A ___ . _____ pints

Milk B ___ . _____ pints

Milk C ___ . _____ pints

Q23 Have you added sugar to tea and coffee or breakfast cereals in the past three months?

No

Yes (go to Q24)

Q24 Approximately how many teaspoons of sugar have you added each day? _____

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The Graham Roberts Study Protocol: a first "Trials within Cohort study" for bladder cancer

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Keywords:	trials within cohorts, bladder cancer, randomised control trial, prospective cohort study

The Graham Roberts Study Protocol: a first "Trials within Cohort study" for bladder cancer

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Abstract

Introduction: Given the need for more bladder cancer research and the recently observed advantages of introducing the trials within cohort (TwiCs) design, the set-up of the Graham Roberts Study (Roberts Study) will provide valuable infrastructure to answer a wide variety of research questions of a clinical, mechanistic, as well as supportive care nature in the area of bladder cancer.

Methods: Using the TwiCs design, we will recruit patients aged 18 or older who are willing and able to provide signed informed consent and have a diagnosis of new or recurrent bladder cancer into this prospective cohort study. All patients must have a basic understanding of the English language. The following questionnaires will be collected at baseline and every 12 months subsequently: Functional assessment of chronic illness therapy for bladder cancer (FACT-Bl), the Functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue), the Patient Heath questionnaire-9 (PHQ-9), the Standardised instrument for a generic health status (EQ-5D-5L), a questionnaire to assess health enhancing physical activity (SQUASH), and the Hertfordshire short questionnaire to assess diet quality.

Ethics and Dissemination: Due to the nature of this study, we obtained full ethical clearance from the London - Fulham Research Ethics Committee (17/LO1975). All participants must provide full informed consent before recruitment onto the study. The results of this study will be published in peer-reviewed journals and data collected as part of the study will be made available to potential collaborators on an application basis.

Keywords: trials within cohorts, bladder cancer, randomised controlled trial, prospective cohort study

Strengths and Limitations

1. First trials within cohort (TwiCs) study design for bladder cancer.
2. TwiCs design generates a wide variety of research opportunities with limited risk to patients.
3. The non-interventional nature of this study means patient participation may not benefit patients' bladder cancer prognosis or quality of life.

Background

Bladder cancer is the 7th most common cancer in the UK, with c.10,400 patients diagnosed annually (1); c. 50% of patients will survive their cancer for 10 years or more after diagnosis. For the majority of patients, the disease remains indolent following initial treatment, and invasive and burdensome surveillance is required to mitigate the high risk of recurrence (2). However, there is proportionally less research into bladder cancer compared to breast, prostate or kidney cancer (3). To provide the most efficient and high impact research strategy for bladder cancer patients in the UK, we have established a prospective cohort study of newly diagnosed bladder cancer patients to allow research that can efficiently address clinical, mechanistic, as well as supportive care related questions.

The design of this bladder cancer cohort study is similar to the Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaLuAtion (UMBRELLA) (4), which is based on the TwiCs design introduced by Relton et al. at the University of Sheffield in 2010 (5). It is the first TwiCs design study in the area of bladder cancer.

The use of TwiCs has grown substantially in the last few years, with several new initiatives in the UK. TwiCs, originally introduced as cohort multiple randomised controlled trial design, was introduced to address the problems associated with existing approaches for trials informing routine clinical practice(5). Such shortcomings relate to recruitment, ethics, patient preferences and treatment comparisons. At least six TwiCs studies are currently ongoing in the UK (6).

The Roberts Study will serve as a facility for multiple trials and follows the TwiCs design.

The main objectives of the Graham Roberts study (Roberts Study) are:

- To create a prospective cohort study of well-characterised bladder cancer patients, which provides the opportunity to conduct a variety of observational studies.
- To create the infrastructure for future RCTs that will allow more efficient recruitment using patient-centred informed consent

Methods/Design

TwiCs design

The TwiCs design can be described as follows: Firstly, a large observational cohort of patients with the condition of interest is recruited and their outcomes regularly measured. Then for each randomised controlled trial (RCT), information from the cohort is used to identify all eligible patients. Some eligible patients are randomly selected and offered the trial intervention. The outcomes of these randomly selected patients are then compared with the outcomes of eligible patients not randomly selected, that is, those receiving usual care. This process can be repeated for further randomised controlled trials (5).

The recruitment and regular follow-up of a large cohort of patients are characteristics of longitudinal observational studies. In the TwiCs design, however, all patients in the cohort consent at the outset to provide data to be used to look at the benefits of treatments for the condition of interest. The capacity for multiple RCTs over time using patients from the same cohort is unique to the TwiCs design. Random selection of some eligible cohort patients, the comparison of their outcomes with the outcomes in eligible patients not randomly selected and the similarity of the patient-centred

informed consent approach to real life situations offer solutions to the ethical criticisms of randomised consent designs (5).

The Graham Roberts Study

Patients will be recruited at Guy's and St Thomas' (GSTT) NHS Foundation Trust, London, UK. All patients will be eligible for the study following their first visit for a new or recurrent bladder cancer diagnosis. Patients with limited understanding of the English language and patients under the age of 18 years are ineligible. Since Guy's and St Thomas NHS Foundation Trust is a referral centre, the Roberts Study will include patients from various secondary and tertiary hospitals located across the United Kingdom. Each year, approximately 100 eligible patients visit the Urology Centre of GSTT for bladder cancer management.

All eligible patients who have already undergone diagnostic investigations and been informed about a (highly likely) bladder cancer will receive detailed written information about the Roberts Study whilst attending the Urology Centre for their initial appointment. They will be scheduled to see a member of the direct clinical care team and a research nurse/assistant 30 minutes prior to their first appointment with the Consultant (urology or oncology). During this research consultation, the research nurse/assistant will explain the study in detail and written informed consent will be obtained from those who agree to participate. Such consent will be gained to allow:

- Participation in the Graham Roberts Study cohort and longitudinal study;
- The participant to be approached to participate in the intervention arm of any future randomised control trial;
- The participant to be randomised to the control arm of any future randomised control trial without knowledge of this status.
- Collection and storage of participants biological samples, including blood, urine and tissue, within the KHP Bladder Cancer Biobank;

- Linkage and use of participants routinely collected clinical data as recorded in electronic patient records.

At the time of full informed consent, the patients will also be provided with the study baseline questionnaire and asked to complete this at a convenient time.

For those eligible patients who have not yet been informed about their bladder cancer diagnosis at the time of visiting the Urology Centre, detailed written information about the Roberts Study will be provided by a research nurse/assistant after they have met with the consultant. If the patients are not ready to discuss this study in further detail at this point, a follow-up call will be made one week later to obtain their consent, if they have agreed to participate. Full written informed consent is subsequently obtained at the patients next clinical appointment.

Data from all patients may be used for observational studies in the Roberts Study, but only those who provide consent for randomisation are eligible for participation in the RCTs within the Roberts Study.

Thus, the TwiCs design is based on an “asymmetric informed consent”. After recruitment into the Roberts cohort, randomisation of eligible subjects, can be followed by an asymmetric treatment of the two arms; those selected for the experimental arm provide informed consent for the intervention trial, while the data from the control arm are used based on prior broad permission. Hence, the cohort participants are informed about future research within the cohort.

Selection and withdrawal of subjects

Patients eligible to participate in this study are those who meet all of the following inclusion criteria:

- Appointment for a new or recurrent diagnosis of bladder cancer at Guy's and St Thomas' NHS Foundation Trust
- Minimum age of 18 years
- Basic understanding of English

Patients will be identified in multi-disciplinary team meetings or in out-patient clinics by the clinical team, in collaboration with the research nurse. Participants have the right to withdraw from the study at any time for any reason. Their routine medical and surgical care will not be affected.

Expected duration of the study and sample size

As this study is an observational prospective cohort study, it is difficult to estimate its duration. We aim to recruit a minimum of 400 patients over a period of 5 years, though there is no limit to the number of patients needed for a prospective cohort study. Moreover, over time new research opportunities will develop and potential funding may become available to continue recruitment into the Roberts Study. Patients will be followed up for life through data linkages with Hospital Episode Statistics (HES), the Office for National Statistics (ONS) and electronic patient records.

As this is a prospective cohort study, with no specific primary research question, it is not possible to perform sample size calculations. However, it is still important to consider recruitment rates and response rates to the questionnaires.

Recruitment to the Graham Roberts Study commenced on 23rd March 2018. At the point of submission of this protocol (April 2019), 84 bladder cancer patients had been approached with a patient information sheet, and 72 patients had provided full written informed consent and completed the baseline study questionnaire. At current rates of consent, the authors project the baseline recruitment of 400 bladder cancer patients to be complete by 31st August 2023. It is expected, however, that recruitment rates will increase as the direct clinical care team and research

nurses/assistants become more efficient at identifying and approaching eligible patients. The projected end of recruitment date is therefore set at 31st December 2022. Moreover, ethical clearance is in place to recruit until this date.

Data collection

Within the Roberts Study, various clinical data will be prospectively collected including demographics, tumour characteristics, treatment and CT and MRI imaging data. Clinical data will be captured from electronic medical records, referral letters and annual reports for Public Health England.

Socio-demographic data will include sex, date of birth, age at diagnosis, highest level of education, postal code (to estimate the deprivation index), body mass index (BMI) and WHO performance status.

The following tumour characteristics will be collected: TNM stage, grade, tumour diameter, number of tumours, histology and morphological codes and invasiveness.

Treatment characteristics comprise data on type and timing of treatment given (e.g. intravesical instillations, systemic chemotherapy, radical cystectomy, radiotherapy or other treatments). Additional detailed data, as reported in surgical notes, will be available for those bladder cancer patients who undergo radical cystectomy. Table 1 illustrates the pre-, peri- and postoperative variables which will be collected for this patient subset.

Table 1: Data collection for those participants of the Roberts Study undergoing radical cystectomy

.Preoperative	TNM stage, weight, height, BMI, American Society of Anesthesiologists (ASA) score, previous pelvic surgery, radiation or neoadjuvant chemotherapy
Perioperative	Type of surgery, type of lymphadenectomy, type of urinary diversion, blood loss, duration of surgery, accidental organ injury during surgery
Postoperative	Complications (Clavien-Dindo), re-operations and re-admissions within 90 days, length of hospital stay, pT stage, number of excised lymph nodes and number of excised and metastatic lymph nodes

Information on disease progression, recurrence and survival will be collected annually by means of the data linkages with HES, ONS and electronic patient records. We will also collect patient-reported outcome measures (PROMs) by means of validated questionnaires designed to quantify health-related Quality of Life (QoL) from the patients' perspective. These questionnaires will be given (paper (post) or digital (email or tablet in clinic)) to patients upon entry into the cohort (baseline) and every 12 months thereafter with a total follow-up of at least 10 years. It will take about 30 minutes to fill out the set of questionnaires at each time point.

PROMs will be collected on QoL, fatigue, anxiety and depression, physical activity, dietary habits as well as risk behaviour in terms of known bladder cancer risk factors. Following an assessment of smoking behaviour, alcohol consumption and occupational bladder cancer risk factors, the following validated questionnaires will be used (see Additional File 1):

- **Quality of Life:** Functional assessment of chronic illness therapy for bladder cancer (FACT-Bl (7))
- **Fatigue:** Functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue (8))
- **Depression:** Patient health questionnaire-9 (PHQ-9 (9))
- **Health** : Standardised instrument for use as a measure of health outcome (EQ-5D-5L(10))
- **Physical activity**: Questionnaire to assess health enhancing physical activity (SQUASH (11))

- **Assessment of dietary habits:** Short questionnaire to assess diet quality (12)

Assessment of safety

As this is a prospective cohort study with no specific interventions, adverse events (AEs) are unlikely to take place. Nevertheless, if filling out questionnaire data should ever result in an AE, it will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 and coded. These will be reported to the Data Monitoring Committee.

Given that we see on average about 100 eligible patients per year, we expect to recruit at least 400 patients over a period of five years. However, as described above, if more research and/or funding opportunities come up, we will continue recruitment into the Roberts study.

Patient and Public Engagement

The development of the Graham Roberts Study was informed in collaboration with patient representatives diagnosed and treated at Guy's and St Thomas' NHS Foundation Trust. Prior to development of the study protocol, a focus group was held to discuss the acceptability of the TwiCs study design and the content of the self-administered questionnaire. Patients of similar bladder cancer diagnoses to those that will be consented onto the study were recruited into this focus group. Based on the patient's experiences and preferences, the Graham Roberts Study design was agreed. Results of the study will be disseminated to the patients through annual newsletters and on a study specific website for patients.

Direct Access to Source Data and Documents

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each patient in the Roberts Study. Study personnel will enter data from source documents corresponding to a patient's visit into the protocol-specific electronic case report forms (CRFs) in a dedicated, secure data warehouse. Patients

will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or Designee), but will be identified by patient ID numbers.

The database will be safeguarded against unauthorised access with established security procedures; nightly backup of the database and related software files will be maintained. At pre-specified junctures of the protocol (e.g., production of interim and final reports), data for analysis will be locked and cleaned as per established procedures.

If a correction is required to a CRF, the time and date stamps will track the person entering or updating CRF data and create an electronic audit trail. The Chief Investigator is responsible for reviewing all information collected on patients enrolled in this study for completeness and accuracy.

To enable evaluations and/or audits from regulatory authorities, the CI agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g. CRFs and hospital records), all original signed informed consent forms, safety reporting forms, source documents and detailed records of treatment disposition and adequate documentation of relevant correspondence (e.g. letters, meeting minutes, telephone call reports). The records should be retained by the CI according to the International Conference on Harmonisation (ICH) or local regulations; all study documentation must be retained for 10 years after the study ends.

Quality Assurance

Monitoring of this study will be performed to ensure compliance with Good Clinical Practice, and scientific integrity will be managed and oversight retained by the Data Monitoring Committee (DMC) led by Prof Dominique Michaud. The committee will receive notification every 6 months of the interim and total accrual. At the discretion of the chair of the DMC, interim analyses may be

scheduled as modifications to the protocol. Additional meetings during the study period may occur at the discretion of the Steering Committee.

The study design, analysis and reporting will follow the recent recommendations for good practice in clinical outcomes assessment by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (13).

Data handling

The Chief Investigator and delegates are responsible for daily cohort management. Data quality will be checked periodically. The following guidelines will be strictly adhered to:

- Patient data will be anonymised.
- All anonymised data will be stored on a password protected encrypted computer.
- All study data will be stored in line with the Data Protection Act as defined in the King's Health Partners' Clinical Trials Office Archiving SOP.

The data will be stored as outlined in the data management plan.

Insurance/Indemnity

The co-sponsors King's College London and Guy's and St Thomas' NHS Foundation Trust will provide insurance and indemnity.

Discussion

The Graham Roberts study is the first of its kind and thus the first TwiCs study for bladder cancer. It generates a wide variety of research opportunities with limited risk to patients. Participation in research involves some loss of privacy. We will do our best to make sure that all personal information gathered for this study is kept private. As this is a non-interventional prospective cohort

study, participation may not have a beneficial effect on patients' bladder cancer prognosis or quality-of-life compared to usual care.

The questionnaires to be used are quite detailed and, for the most part, concerns day-to-day activities such as quality and duration of sleep, diet and exercise. The questionnaire does pose some more personal and intrusive questions however, including questions related to symptoms of depression. These questions can be omitted if the participant does not feel comfortable answering them. There is a risk that some participants may be upset by having these questions posed to them. Some participants may prefer to complete the questionnaire themselves, whereas others may prefer to do so with a research assistant. Participants will be fully informed about these potential harms and enabled to make an informed decision regarding participation. We consider that the potential minor harms are outweighed by the potential benefits of the research.

Future research using the data in this study could lead to medical and scientific products, discoveries, as well as interventions that improve the prevention, diagnosis and treatment of bladder cancer. A benefit for the patients is also the possibility to be part of future RCTs by providing consent for being part of the intervention arm.

Trial Status

Protocol Version and Number: Version 2, January 2018

Date of commencement of recruitment: 23rd March 2018

Projected date of recruitment completion: 31st December 2022

Ethics and Dissemination

The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP, and in accordance with all applicable regulatory requirements including but

not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments. This protocol and related documents were approved by the London – Fulham Research Ethics Committee (REC) as part of gaining Health Research Authority (HRA) approval (17/LO/1975).

After completion of an RCT within the Roberts Study, all patients – irrespective of participation in the specific study – will receive aggregated results via a newsletter that they can subscribe to at time of initial consent. All results associated with this study will be published in journals as peer-reviewed articles.

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Additional Files

Additional File 1 – Graham Roberts Study Questionnaire (doc).
The questionnaire given to patients who have consented to the Graham Roberts Study.

List of abbreviations

AE	Adverse events
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CI	Chief Investigator
CRF	Case Research Form
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
EQ-5D-5L	Standardised instrument for use as a measure of health outcome
FACT-Bl	Functional assessment of chronic illness therapy for bladder cancer
FACIT	Functional assessment of chronic illness therapy - fatigue
GCP	Good Clinical Practice
GSTT	Guy's and St Thomas'
HES	Hospital Episode Statistics
HRA	Health Research Authority
ICH	International Conference on Harmonisation
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KCL	King's College London
NHS	National Health Services
ONS	Office National Statistics
PHQ-9	Patient health questionnaire-9
PI	Principle Investigator
PROMS	Patient-reported outcomes
QoL	Quality of Life
RCT	Randomise Clinical Trial
REC	Research Ethics Committee
SOP	Standard Operating Procedures
SQUASH	Questionnaire to assess health enhancing physical activity
TwiCs	Trials within Cohorts
UK	United Kingdom
WHO	World Health Organisation

Declarations

Ethics approval and consent to participate

The Fulham Research Ethics Committee approved the Graham Roberts Study on 22/02/2018 (Reference number: 17/LO/1975).

Consent for publication

Not applicable.

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests.

Funding

Funding to conduct the study is kindly provided by the Graham and Dianne Roberts Charitable Settlement. The funders had no role in the design of the study and collection, analysis, and interpretation of data nor in writing of the manuscript.

Authors' contributions

MVH, FC, HW, CR, CM, and AS designed the study with input from their clinical colleagues (SC, SH, SR, DE, DJ, RB, SA, KC, SK) and the biobank coordinator (CG). All authors read and approved the final manuscript.

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Graham Roberts Study (Roberts Study)

Patient Questionnaire

Through the Roberts Study, we are learning about why some bladder cancers respond better to treatment than others. This will help us to develop new and better ways of predicting recurrence and progression of bladder cancer in the future, as well as new interventions that can improve quality and quantity of life. Your participation is a critical contribution toward this goal.

This questionnaire is confidential. We will be taking every step to ensure that your answers to the interview questions are stored securely and are not shared with anyone outside the study team.

If you need any help with any of the questions, please feel free to ask the study team.

Participant number: _____

Date of Birth: _____

Date of Questionnaire: _____

Is this the first time you have filled in this questionnaire? Yes/No

*If this is not the first time you have filled in the questionnaire, please skip **section 1 and 2** and proceed immediately to **section 3** below.*

Section 1 – Personal details and medical history

1. **How would you describe your race / ethnic background?**

   White/Caucasian ☐ Black/Afro-Caribbean ☐ Asian ☐ Other ☐

   If other, please specify.....

2. **What is your current marital status?**

   Married ☐ Divorced/Separated ☐ Widowed ☐ Never married ☐

3. **What is your current living arrangement?**

   Alone ☐ With partner ☐ With other family ☐

   Assisted Living ☐ Nursing Home ☐ Other ☐

4. **What is your current work status?**

   Full-time ☐ Part-time ☐ Retired ☐

   Disabled ☐ Unemployed ☐

5. **What is your highest level of education?**

   Primary school ☐ Higher education (e.g. University) ☐

   Secondary school ☐ Other ☐

For the following questions please circle or tick the appropriate answer:

6. **Have you ever had any type of cancer (except for non-melanoma skin cancer)?**

   YES NO
   If you answered yes, please specify: _____

7. **Were any of your immediate blood relatives, that is, your mother, or father, or sister(s), or brother(s), or son(s), or daughter(s), ever diagnosed as having any type of cancer?**
   - □ Yes
   - □ No – please continue to question 8
   - □ I prefer not to answer
   - □ I don't know

   Who was/were diagnosed as having cancer, that is, what was his or her relationship to you?
   - □ Mother
   - □ Father
   - □ Brother(s)
   - □ Sister(s)
   - □ Son(s)
   - □ Daughter(s)
   - □ I prefer not to answer
   - □ I don't know

   You indicated that at least one of your immediate blood relatives was diagnosed with cancer. Was he/she, or at least one of them (if more than one), diagnosed with **bladder cancer**?
   - □ Yes
   - □ No
   - □ I prefer not to answer
   - □ I don't know

8. **Did you ever have a bladder infection with at least one of the following symptoms: frequent urination or pain or burning when urinating?**
   - □ Yes
   - □ No
   - □ I prefer not to answer
   - □ I don't know

   How many times did you have this kind of infection? Would you say:
   - □ 1 or 2 times,
   - □ 3 or 5 times,
   - □ 6 or 10 times,
   - □ 11 or more times?
   - □ I prefer not to answer
   - □ I don't know

   How old were you when you first had this type of infection?
   When I was _____ years old
   - □ I prefer not to answer
   - □ I don't know

9. Did you ever have a kidney infection diagnosed by a physician?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

How many times did you have this kind of infection? Would you say:

- □ 1 or 2 times,
- □ 3 or 5 times,
- □ 6 or 10 times,
- □ 11 or more times?
- □ I prefer not to answer
- □ I don't know

10. Before 1 year ago, did you ever have renal or nephritic colic, or kidney or renal stones?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

11. Before 1 year ago, did you ever have urinary bladder stones?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

12. Before 1 year ago, did you ever have a growth removed from your urinary bladder?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

13. Did you ever have any of the following symptoms when urinating: difficulty starting, difficulty stopping or increased frequency during the night?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

14. If you are a man, please answer the following question: Did your doctor ever tell you that you had an enlarged prostate?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

[Women only] The next group of questions are about your reproductive history. Firstly, how old were you when you had your first menstrual period?

[ ] years old

- □ I prefer not to answer
- □ I don't know

Have you had at least one menstrual period in the past 12 months?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

Are you pregnant or breastfeeding?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

Have you had surgery to remove your uterus (hysterectomy)?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

Have you had any of your ovaries surgically removed (oophorectomy)?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

How many of your ovaries were removed?

- □ One
- □ Both
- □ I prefer not to answer
- □ I don't know

Have you ever taken birth control pills?

- □ Yes
- □ No
- □ I prefer not to answer
- □ I don't know

At what age did you first start taking birth control pills?

_____ year old

- □ I prefer not to answer
- □ I don't know

How long did you take birth control pills?

_____ years _____ months

- □ I prefer not to answer
- □ I don't know

How many times have you been pregnant?

- □ Never
- □ _____ times
- □ I prefer not to answer
- □ I don't know

How many of your pregnancies ended in a live birth?

_____

- □ I prefer not to answer
- □ I don't know

Section 2 – History of tobacco consumption

Please tick the most appropriate answer:

1. **During your entire lifetime, have you smoked a total of 100 cigarettes or more, which is 5 or more packs?**
   - □ Yes
   - □ No
   - □ I prefer not to answer
   - □ I don't know

2. **Did you ever smoke cigarettes regularly, that is, at least one per day for six months or longer?**
   - □ Yes
   - □ No
   - □ I prefer not to answer
   - □ I don't know

3. **Think about all the years that you smoked cigarettes, how many cigarettes per day did you usually smoke?**
   - □ Less than one
   - □ _____
     [please enter a number if it is more than 1, but less than 95]
   - □ More than 95
   - □ I prefer not to answer
   - □ I don't know

4. **How old were you when you first started smoking at least one cigarette per day?**
   years old
   - □ I prefer not to answer
   - □ I don't know

5. **How old were you when you last smoked cigarettes?**
   _____ years old
   - □ I still smoke
   - □ I refuse to answer
   - □ I don't know

6. **When you smoked cigarettes, would you say that you usually inhaled only into your mouth, into your mouth and throat or into your chest?**
   - □ Mouth only
   - □ Mouth and throat
   - □ Chest
   - □ I do not inhale
   - □ Cannot say, but not deeply into the chest
   - □ I prefer not to answer
   - □ I don't know

7. **Have you ever smoked at least one cigar per week for six months or longer?**
   - □ Yes
   - □ No
   - □ I prefer not to answer
   - □ I don't know

8. How old were you when you first started smoking at least one cigar per week?

_____ years old

□ I refuse to answer

□ I don't know

9. How old were you when you last smoked cigars?

_____ years old

□ I still smoke cigars

□ I refuse to answer

□ I don't know

10. For how many years altogether have you smoked/did you smoke cigars? Please do not include any periods during which you may have quit.

_____ years _____ months

□ I don't know

□ I prefer not to answer

11. Thinking about all the years that you smoked cigars, how many cigars did you usually smoke in a week?

□ Less than one

□ _____

[please enter a number if it is more than 1 but less than 95]

□ More than 95

□ I refuse to answer

□ I don't know

12. Have you ever smoked at least one pipe of tobacco per week for six months or longer?

□ Yes

□ No

□ I prefer not to answer

□ I don't know

13. How old were you when you first started smoking at least one pipe of tobacco per week?

_____ years old

□ I refuse to answer

□ I don't know

14. How old were you when you last smoked a pipe?

_____ years old

□ I still smoke a pipe

□ I refuse to answer

□ I don't know

Section 3 – Current medical conditions and medications

1. Have you been diagnosed with any of the following medical conditions?'

(a) High blood pressure	YES	NO
(b) Diabetes mellitus	YES	NO
(c) High cholesterol	YES	NO
(d) Myocardial infarction (heart attack)	YES	NO
(e) Angina pectoris	YES	NO
(f) Atrial fibrillation	YES	NO
(g) Congestive heart failure	YES	NO

2. Have you regularly taken any of these medications *in the last two years*?

(a) Non-steroidal anti-inflammatory drugs (NSAIDs)

(i) Aspirin	YES	NO
(ii) Ibuprofen (e.g. Advil, Nurofen, Nuprin, Medipren)	YES	NO
(iii) Other: _____	YES	NO

(b) "Statin" cholesterol-lowering drugs

(i) Lovastatin (e.g. Mevacor, Altocor)	YES	NO
(ii) Simvastatin (e.g. Zocor)	YES	NO
(iii) Pravastatin (e.g. Pravachol, Pravigard)	YES	NO
(iv) Atorvastatin (e.g. Lipitor)	YES	NO
(v) Other: _____	YES	NO

(c) Beta blocker drugs

(i) Metoprolol (e.g. Lopressor, Toprol)	YES	NO
(ii) Atenolol (e.g. Tenormin)	YES	NO
(iii) Nadolol (e.g. Corgard)	YES	NO
(iv) Other: _____	YES	NO

(d) Antidepressants: Selective serotonin reuptake inhibitors (SSRIs)

(i) Citalopram (e.g. Celexa)	YES	NO
(ii) Escitalopram (e.g. Lexapro)	YES	NO
(iii) Fluoxetine (e.g. Prozac)	YES	NO
(iv) Paroxetine (e.g. Paxil)	YES	NO
(v) Sertraline (e.g. Zoloft)	YES	NO
(vi) Fluvoxamine (e.g. Luvox)	YES	NO
(vii) Other: _____	YES	NO

(e) Other antidepressants

(i) Amitriptyline (e.g. Elavil, Endep)	YES	NO
(ii) Imipramine (e.g. Tofranil)	YES	NO
(iii) Nortriptyline (e.g. Pamelor)	YES	NO
(iv) Other: _____	YES	NO

(f) Sleeping tablets

(i) Diazepam (e.g. Valium)	YES	NO
(ii) Alprazolam (e.g. Xanax)	YES	NO
(iii) Lorazepam (e.g. Ativan)	YES	NO
(iv) Chlordiazepoxide (e.g. Librium)	YES	NO
(v) Other: _____	YES	NO

(g) Diabetes medications

(i) Insulin	YES	NO
(ii) Metformin	YES	NO
(iii) Rosiglitazone (e.g. Avandia)	YES	NO
(iv) Pioglitazone (e.g. Actos)	YES	NO
(v) Other: _____	YES	NO

(h) Are you on any other long-term medication? _____

Section 4 – Current smoking behaviour, alcohol consumption and other environmental/occupational exposures

Please circle the most appropriate answer:

1. **Do you currently smoke cigarettes, a pipe or cigars? If you answered YES, how many cigarettes, pipe refills or cigars do you smoke per day?**

	Cigarettes		Pipe		Cigars	
Currently smoke?	YES	NO	YES	NO	YES	NO
If yes, how many per day?	1-4 5-14 15-24 25-34 35-44 45 or more		1-4 5-10 10 or more		1-4 5-10 10 or more	

2. **In a typical week over the past three months, on how many days did you consume an alcoholic drink of any type?**

No days *1 day per week* *2 days per week* *3 days per week*

4 days per week *5 days per week* *6 days per week* *7 days per week*

3. **In a typical month, what is the largest number of drinks of beer, wine and / or spirits you have in one day?**

None *1-2 drinks per day* *3-5 drinks per day*

6-9 drinks per day *10-14 drinks per day* *15 or more drinks per day*

4. **On a typical day, what is the total number of alcoholic and non-alcoholic drinks combined you have in one day?**

1-*2 pints per day* *3-5 pints per day*

6-9 pints per day *10-14 pints per day* *15 or more pints per day*

5. **On a typical day, how many cups of coffee do you drink in one day?**

None 1-*2 cups per day* *3-5 cups per day*

6-9 cups per day *10 or more cups per day*

6. **Have you ever worked in the production of rubber or aluminium or were you exposed to aromatic amines (eg. printing or dye industry) for five years or more?** YES NO

7. **Do you get your drinking water from a private well?** YES NO

Section 5 – Quality of Life (FACT-BI)

Below is a list of statements that other people have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BL1	I have trouble controlling my urine	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
C5	I have diarrhoea	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BL3	It burns when I urinate	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BL5	(For men only) I am able to have and maintain an erection	0	1	2	3	4
Q2	Do you have an ostomy appliance? No___ Yes___ If yes, answer the following two items: ↓					
C8	I am embarrassed by my ostomy appliance	0	1	2	3	4
C9	Caring for my ostomy appliance is difficult	0	1	2	3	4

Section 6 – Fatigue (FACIT - Fatigue)

Below is a list of statements that other people have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Section 7 – Anxiety and Depression (PHQ-9)

Over the past 2 weeks, how often have you been bothered by any of the following problems?	Not At all	Several Days	More Than Half the Days	Nearly Every Day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3
3. Trouble falling asleep, staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself - or that you're a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or, the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
Column Totals	_____	+ _____	+ _____	
Add Totals Together	_____			

10. If you checked off any problems, how difficult have those problems made it for you to Do your work, take care of things at home, or get along with other people?

☐ Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult

Section 8 – Health Questionnaire (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

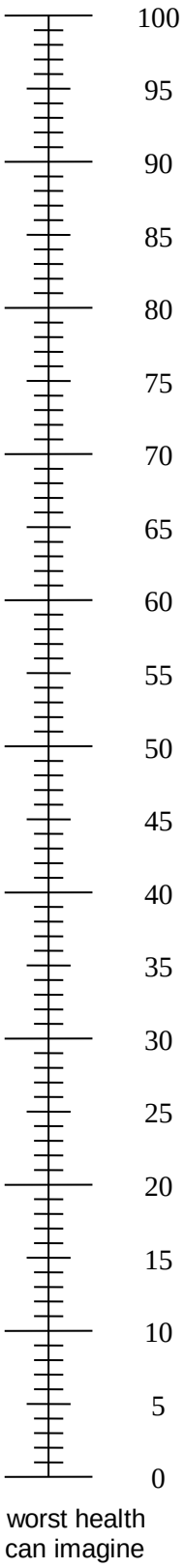
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Section 9 – Physical activity

Think about an average week in the past months. Please indicate **how many days per week** you performed the following activities, how much time on average you were engaged in this, and (if applicable) how strenuous this activity was for you?

	Days per week	Average time per day	Effort (circle please)
Walking	days	hours minutes	slow/moderate/fast
Bicycling	days	hours minutes	slow/moderate/fast
Other physical activity (e.g. swimming, gym, gardening)	days	hours minutes	slow/moderate/fast

If you wear a pedometer on a regular basis, on average how many steps a day to you take?

<2500 steps *2500-4999 steps* *5000-9999 steps*

10000 or more steps *N/A – do not use*

Section 10 – Diet (Hertfordshire Short Questionnaire)

The section below asks you about how often over the past 3 months you have eaten particular foods.

	FOOD AND AMOUNTS	AVERAGE USE IN PAST 3 MONTHS									
		Never	Less than once/month	1-3 per month	Once a week	2-4 pe week	5-6 week	Once a day	2-3 per day	4-5 pe day	6+ per day
1	White bread (one slice)										
2	Brown and wholemeal bread (one slice)										
3	Biscuits eg digestive (one)										
4	Apples (one fruit)										
5	Bananas (one fruit)										
6	Melon, pineapple, kiwi and other tropical fruits (medium serving)										
7	Green salad eg lettuce, cucumber, celery										
8	Garlic – raw and cooked dishes										
9	Marrow and courgettes										
10	Pepper – cooked and fresh										
11	Yogurt (125g pot)										
12	Egg as boiled, fried, scrambled, etc (one egg)										
13	White fish eg cod, haddock, plaice, sole (not in batter/crumbs)										
14	Oily fish, eg mackerel, tuna, salmon										
15	Bacon and gammon										
16	Meat pies, eg pork pie, pasties, steak & kidney, sausage rolls										
17	Boiled, mashed and jacket potatoes (one egg size potato)										
18	Chips										
19	Pasta eg spaghetti, macaroni										
Which is the main spreading fat you have used for example on bread or vegetables?											
20	Spreading fat (teaspoon) _____										

ADDITIONAL DIETARY QUESTIONS

Q21 Which types of milk have you used regularly in drinks and added to breakfast cereals over the past three months? Circle all that apply.

1. Whole pasteurised
2. Semi-skimmed pasteurised (include 1% milks)
3. Skimmed pasteurised
4. Whole UHT
5. Semi-skimmed UHT
6. Skimmed UHT
7. Other: _____ (please specify)
8. None (go to Q23)

Of the above, which are the three types of milk that you drink most commonly?

Number ____ (Milk A)

Number ____ (Milk B)

Number ____ (Milk C)

Q22 On average over the past three months how much of the above have you consumed per day?

Milk A ___ . _____ pints

Milk B ___ . _____ pints

Milk C ___ . _____ pints

Q23 Have you added sugar to tea and coffee or breakfast cereals in the past three months?

No

Yes (go to Q24)

Q24 Approximately how many teaspoons of sugar have you added each day? _____