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

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2
3 **32 Abstract**
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5 **33 Background:** Given the need for more bladder cancer research and the recently observed
6
7 **34** advantages of introducing the trials within cohort (TwiCs) design, the set-up of the Graham Roberts
8
9 **35** Study (Roberts Study) will provide valuable infrastructure to answer a wide variety of research
10
11 **36** questions of a clinical, mechanistic, as well as supportive care nature in the area of bladder cancer.
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14 **37 Methods:** Using the TwiCs design, we will recruit patients aged 18 or older who are willing and able
15
16 **38** to provide signed informed consent and have a diagnosis of an active new or recurrent bladder
17
18 **39** cancer into this prospective cohort study. All patients have to have a basic understanding of the
19
20 **40** English language. The following questionnaires will be collected baseline and every 12 months:
21
22 **41** Functional assessment of chronic illness therapy for bladder cancer (FACT-BI), the Functional
23
24 **42** assessment of chronic illness therapy-fatigue (FACIT-Fatigue), the Patient health questionnaire-9
25
26 **43** (PHQ-9), the Standardised instrument for a generic health status (EQ-5D-5L), a questionnaire to
27
28 **44** assess health enhancing physical activity (SQUASH), and the Hertfordshire short questionnaire to
29
30 **45** assess diet quality.
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33
34 **46 Discussion:** The main outcome of this work will thus be a well-annotated cohort of bladder cancer
35
36 **47** patients that provides the opportunity to address a wide variety of important research questions. It
37
38 **48** will also allow the efficient set-up of new randomised controlled trials (RCTs) for bladder cancer
39
40 **49** patients (e.g. a smoking cessation intervention), whilst making use of the linkage with our existing
41
42 **50** King's Health Partners' Bladder Cancer Biobank.
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46 **51**

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48
49 **53 Keywords:** trials within cohorts, bladder cancer, randomised controlled trial, prospective cohort

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51 **54** study
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58 **Strengths and Limitations**

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

66 **Background**

67 Bladder cancer is the 7th most common cancer in the UK, with c.10,400 patients diagnosed annually
68 [1]; c. 50% of patients will survive their cancer for 10 years or more after diagnosis. For the majority
69 of patients, the disease remains indolent following initial treatment, and invasive and burdensome
70 surveillance is required to mitigate the high risk of recurrence [2]. However, there is proportionally
71 less research into bladder cancer compared to breast, prostate or kidney cancer [3]. To provide the
72 most efficient and high impact research strategy for bladder cancer patients in the UK, we have
73 established a prospective cohort study of newly diagnosed bladder cancer patients to allow research
74 that can efficiently address clinical, mechanistic, as well as supportive care related questions. The
75 main outcome of this work will thus be a well-annotated cohort of bladder cancer patients that
76 provides the opportunity to address a wide variety of important research questions. It will also allow
77 the efficient set-up of new randomised controlled trials (RCTs) for bladder cancer patients (e.g. a
78 smoking cessation intervention), whilst making use of the linkage with our existing King's Health
79 Partners' Bladder Cancer Biobank.

80
81 The design of this bladder cancer cohort study is similar to the Utrecht cohort for Multiple BREast
82 cancer intervention studies and Long-term evaLuAtion (UMBRELLA) [4], which is based on the TwICs

1
2
3 83 design introduced by Relton et al. at the University of Sheffield in 2010 [5]. It is the first TwiCs design
4
5 84 study in the area of bladder cancer. More information about the TwiCs design can be found below.
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9
10 86 The use of TwiCs has grown substantially in the last few years, with several new initiatives in the UK.
11
12 87 A 2015 systematic review identified 16 studies implementing the TwiCs design, with a total of 18
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14 88 ongoing or completed trials embedded within these cohorts [6]. Some cohorts focused on a single
15
16 89 disease or injury (e.g. hip fracture, breast cancer, colorectal cancer), whilst others had a wider focus
17
18 90 (e.g. risk of mental health conditions, risk of falls). Some studies built a cohort around a trial, and
19
20 91 then obtained further funds to exploit the cohort for further trials within that cohort. At least six
21
22 92 TwiCs studies are ongoing in the UK [7], of which one is the Yorkshire Health Study [8]. The latter is
23
24 93 a longitudinal observational regional health study collecting health information on the residents of
25
26 94 the Yorkshire and Humberside region in England [8]. The study principally aims to inform National
27
28 95 Health Service (NHS) and local authority health-related decision making in Yorkshire, but with
29
30 96 additional wider implications from the findings as well.
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39 97
36 98 The main objectives of the Graham Roberts study (Roberts Study) are:

- 39 99 • To create a prospective cohort study of well-characterised bladder cancer patients, which
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41 100 provides the opportunity to conduct a variety of observational studies.
- 43 101 • To create the infrastructure for future RCTs that will allow more efficient recruitment using
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45 102 patient-centred informed consent
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50 104 **Methods/Design**

51 52 105 *TwiCs design*

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54 106 TwiCs, originally introduced as cohort multiple randomised controlled trial design, was introduced to
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56 107 address the problems associated with existing approaches for trials informing routine clinical
57
58 108 practice [5]. The design can be described as follows: Firstly, a large observational cohort of patients
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3 109 with the condition of interest is recruited and their outcomes regularly measured. Then for each
4
5 110 randomised controlled trial (RCT), information from the cohort is used to identify all eligible
6
7 111 patients. Some eligible patients are randomly selected and offered the trial intervention. The
8
9 112 outcomes of these randomly selected patients are then compared with the outcomes of eligible
10
11 113 patients not randomly selected, that is, those receiving usual care. This process can be repeated for
12
13 114 further randomised controlled trials [5].
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18
19 116 The recruitment and regular follow-up of a large cohort of patients are characteristics of longitudinal
20
21 117 observational studies. In the TwiCs design, however, all patients in the cohort consent at the outset
22
23 118 to provide data to be used to look at the benefits of treatments for the condition of interest. The
24
25 119 capacity for multiple RCTs over time using patients from the same cohort is unique to the TwiCs
26
27 120 design. Random selection of some eligible cohort patients, the comparison of their outcomes with
28
29 121 the outcomes in eligible patients not randomly selected and the similarity of the patient-centred
30
31 122 informed consent approach to real life situations offer solutions to the ethical criticisms of
32
33 123 randomised consent designs [5].
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37 124

38 39 125 *The Graham Roberts Study*

40
41 126 Patients will be recruited at Guy's and St Thomas' (GSTT) NHS Foundation Trust, London, UK. All
42
43 127 patients following their first visit for their active new or recurrent bladder cancer will be eligible.
44
45 128 Patients with limited understanding of the English language and patients under the age of 18 years
46
47 129 are ineligible. Since Guy's Hospital is a referral centre the Roberts Study will include patients from
48
49 130 secondary and tertiary hospitals. Each year, approximately 100 eligible patients visit GSTT for
50
51 131 bladder cancer management.
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56 133 All eligible patients who have already been informed about a (highly likely) bladder cancer at the
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58 134 time of visiting the Urology Centre, will receive detailed written information about the Roberts Study
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3 135 whilst waiting for their appointment. They will then be scheduled to see a member of the direct
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5 136 clinical care team and a research nurse/assistant 30 minutes prior to their first appointment with the
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7 137 Consultant (urology or oncology). During this research consultation, the research nurse/assistant will
8
9 138 explain the study in detail and written informed consent will be obtained from those who agree to
10
11 139 participate. At this time, the patients will also be asked to fill out the baseline questionnaire.
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16 141 For those eligible patients who have not yet been informed about their bladder cancer at the time of
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18 142 visiting the Urology Centre, detailed written information about the Roberts Study will be provided by
19
20 143 a research nurse/assistant after they have met with the consultant. If the patients are not ready to
21
22 144 discuss this study in further detail, a follow-up call will be made one week later to obtain their
23
24 145 consent, if they have agreed to participate.
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28
29 147 The Roberts Study will serve as a facility for multiple trials and follows the TwiCs design. In this
30
31 148 context, informed consent will be obtained through a staged procedure [9]. Before entering the
32
33 149 cohort, all patients give written informed consent for collection and use of their clinical data.
34
35

36 150 Patient-reported outcomes (PROMs) and other relevant questionnaires are collected at baseline and
37
38 151 at fixed intervals during follow-up. At this stage, the patients will also be invited to consent for the
39
40 152 King's Health Partner's Cancer Biobank – allowing for a link between the Roberts Study and their
41
42 153 biospecimen collection. However, consent to the Biobank is not a requirement for participating in
43
44 154 the Roberts Study.
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49 156 In addition, patients may give consent to be randomly allocated to experimental intervention
50
51 157 relating to bladder cancer in the (near) future. Only those patients randomly allocated to the
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53 158 intervention arm will be offered the experimental intervention (which they can accept or decline). If
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55 159 they accept, additional written informed consent to undergo the experimental intervention will be
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57 160 obtained. Patients who decline intervention will receive standard of care, which will be unaffected
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3 161 by the fact they have declined to participate in the randomised element of this study. Patients who
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5 162 are randomly allocated to the control arm will also receive standard of care, and are not informed
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7 163 about their participation in the control arm. This additional consent will be obtained at the time of
8
9 164 consent for the cohort study.
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14 166 Data from all patients may be used for observational studies in the Roberts Study, but only those
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16 167 who provide consent for randomisation are eligible for participation in the RCTs within the Roberts
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18 168 Study. After completion of an RCT within the Roberts Study, all patients – irrespective of
19
20 169 participation in the specific study – will receive aggregated results via a newsletter that they can
21
22 170 subscribe to at time of initial consent.
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28 172 Thus, the TwiCs design is based on an “asymmetric informed consent”. After recruitment into the
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30 173 Roberts cohort, randomisation of eligible subjects, can be followed by an asymmetric treatment of
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32 174 the two arms. Those selected for the experimental arm provide informed consent for the
33
34 175 intervention trial, while the data from the control arm are used based on prior broad permission.
35
36 176 Hence, the cohort participants are informed about future research within the cohort.
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40 41 178 *Patient and Public Engagement*

42
43 179 The development of the Graham Roberts Study was informed in collaboration with patient
44
45 180 representatives diagnosed and treated at Guy’s and St Thomas’ NHS Foundation Trust. Prior to
46
47 181 development of the study protocol, a focus group was held to discuss the acceptability of the TwiCs
48
49 182 study design and the content of the self-administered questionnaire. Patients of similar bladder
50
51 183 cancer diagnoses to those that will be consented onto the study were recruited into this focus
52
53 184 group. Based on the patient’s experiences and preferences, the Graham Roberts Study design was
54
55 185 agreed. Results of the study will be disseminated to the patients through annual newsletters and on
56
57 186 a study specific website for patients.
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3 187 *Selection and withdrawal of subjects*
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5 188 Patients eligible to participate in this study are those who meet all of the following inclusion criteria:
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7
8 189 • Appointment for an active new or recurrent bladder cancer diagnosis at Guy's and St Thomas'
9

10 190 NHS Foundation Trust
11

12 191 • Minimum age of 18 years
13

14 192 • Basic understanding of English
15

16
17 193 Patients must NOT meet any of the following exclusion criteria:
18

19 194 • Younger than 18 years
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21 195 • Limited understanding of English
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26 197 Patients will be identified in multi-disciplinary team meetings or in out-patient clinics by the clinical
27

28 198 team, in collaboration with the research nurse. Participants have the right to withdraw from the
29

30 199 study at any time for any reason. Their routine medical and surgical care will not be affected.
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35 201 *Expected duration of the study*
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37 202 As this study is an observational prospective cohort study, it is difficult to estimate its duration. We
38

39 203 aim to recruit a minimum of 400 patients over a period of 5 years, though there is no limit to the
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41 204 number of patients needed for a prospective cohort study. Moreover, over time new research
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43 205 opportunities will develop and potential funding may become available to continue recruitment into
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45 206 the Roberts Study. Patients will be followed up for life through data linkages with Hospital Episode
46

47 207 Statistics (HES), the Office for National Statistics (ONS) and electronic patient records.
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52 209 *Study procedures by visit*
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54 210 All potentially eligible patients who already know they have bladder cancer will receive detailed
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56 211 written information about the Roberts Study whilst they are waiting for their appointment. They will
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58 212 be scheduled to see a member of the direct clinical care team and a research nurse/assistant 30
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3 213 minutes prior to their appointment with the consultant (urology or oncology). During this research
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5 214 consultation, the research nurse/assistant will explain the study in detail, and written informed
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7 215 consent for entering the cohort and potential entry into an intervention arm will be obtained from
8
9 216 those who agree to participate. Patients who require more time to consider their consent, will be
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11 217 given this time and will be approached at their next scheduled clinical visit. If at that time they do
12
13 218 not want to consent, patients will not be approached again.
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19 220 For those eligible patients who have not yet been informed about their bladder cancer at the time of
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21 221 visiting the Urology Centre, detailed written information about the Roberts Study will be provided by
22
23 222 a research nurse/assistant after they have met with the consultant. If the patients are not ready to
24
25 223 discuss this study in further detail, they will be given more time to consider their consent and will be
26
27 224 approached again at their next scheduled clinical visit. If at that time they do not want to consent,
28
29 225 patients will not be approached again.
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33 226
34 227 Following this consent (baseline), the patients will be given a variety of questionnaires either on
35
36 228 paper or digital (tablet). It will take about 30 minutes to fill out the set of questionnaires at the
37
38 229 respective time point. Every 12 months thereafter, with a total follow-up of at least 10 years,
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40 230 patients will be asked to fill out the questionnaires again, which may be sent via post/email or can
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42 231 be filled out in clinic during a regular follow-up visit.
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48 233 If patients agree to also consent for the King's Health Partners Cancer Biobank (which is not a
49
50 234 requirement for being in the Roberts Study) at the time of consenting to the Roberts study, they will
51
52 235 also agree to:

- 53
54 236
- 55 • donate paraffin processed tumour samples for research objectives
 - 56
 - 57 237 • have paraffin embedded blocks archived for research objectives
 - 58

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

242

243 *Data collection*

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

247

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

251

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

254

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

259

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

261

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

269

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

274

- 275 • **Quality of Life:** Functional assessment of chronic illness therapy for bladder cancer (FACT-BI
 276 [11])
- 277 • **Fatigue:** Functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue [12])
- 278 • **Depression:** Patient health questionnaire-9 (PHQ-9 [13])
- 279 • **Health :** Standardised instrument for use as a measure of health outcome (EQ-5D-5L[14])
- 280 • **Physical activity:** Questionnaire to assess health enhancing physical activity (SQUASH [15])
- 281 • **Assessment of dietary habits:** Short questionnaire to assess diet quality [16]

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3 283 *Assessment of safety*
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5 284 As this is a prospective cohort study with no specific interventions, adverse events (AEs) are unlikely
6
7 285 to take place. Nevertheless, if filling out questionnaire data should ever result in an AE, it will be
8
9 286 graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
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11 287 and coded. These will be reported to the Data Monitoring Committee.
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16 289 *Sample size*
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19 290 As this is a prospective cohort study, with no specific primary research question, it is not possible to
20
21 291 perform sample size calculations. However, it is still important to consider recruitment rates and
22
23 292 response rates to the questionnaires. In the Dutch UMBRELLA study, 1,308 out of 1,485 (88%)
24
25 293 patients who were invited consented to cohort participation [4]. Of those, 1,138 (87%) gave consent
26
27 294 for randomisation to future interventions. Return rates for questionnaires at baseline were 80%, and
28
29 295 varied from 67 to 74% during follow-up. Sixty percent of patients chose to fill out the questionnaires
30
31 296 online, while 40% opted for paper questionnaires [4].
32
33

34 297

35
36 298 Given that we see on average about 150 eligible patients per year, we expect to recruit at least 400
37
38 299 patients over a period of five years. However, as described above, if more research and/or funding
39
40 300 opportunities come up, we will continue recruitment into the Roberts study.
41
42

43 301 *Direct Access to Source Data and Documents*
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45 302 The Investigator will prepare and maintain adequate and accurate source documents designed to
46
47 303 record all observations and other pertinent data for each patient in the Roberts Study. Study
48
49 304 personnel will enter data from source documents corresponding to a patient's visit into the
50
51 305 protocol-specific electronic case report forms (CRFs) in a dedicated, secure data warehouse. Patients
52
53 306 will not be identified by name in the study database or on any study documents to be collected by
54
55 307 the Sponsor (or Designee), but will be identified by patient ID numbers.
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3 309 The database will be safeguarded against unauthorised access with established security procedures;
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5 310 nightly backup of the database and related software files will be maintained. It will be backed up by
6
7 311 the database administrator in conjunction with any updates or changes to the database. At pre-
8
9 312 specified junctures of the protocol (e.g., production of interim and final reports), data for analysis
10
11 313 will be locked and cleaned as per established procedures. The data warehouse will be stored on a
12
13 314 secured KCL server and will be managed by a dedicated data scientist for the bladder cancer
14
15 315 research team who has an honorary contract with GSTT.
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21 317 If a correction is required to a CRF, the time and date stamps will track the person entering or
22
23 318 updating CRF data and create an electronic audit trail. The Chief Investigator is responsible for
24
25 319 reviewing all information collected on patients enrolled in this study for completeness and accuracy.
26
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30 321 To enable evaluations and/or audits from regulatory authorities, the CI agrees to keep records,
31
32 322 including the identity of all participating subjects (sufficient information to link records, e.g. CRFs
33
34 323 and hospital records), all original signed informed consent forms, safety reporting forms, source
35
36 324 documents and detailed records of treatment disposition and adequate documentation of relevant
37
38 325 correspondence (e.g. letters, meeting minutes, telephone call reports). The records should be
39
40 326 retained by the CI according to the International Conference on Harmonisation (ICH) or local
41
42 327 regulations; all study documentation must be retained for 10 years after the study ends.
43
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328

47 329 *Ethics and Regulatory Approvals*

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49
50 330 The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996),
51
52 331 the principles of GCP, and in accordance with all applicable regulatory requirements including but
53
54 332 not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial)
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56 333 Regulations 2004, as amended in 2006 and any subsequent amendments.
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3 335 This protocol and related documents were approved by the London – Fulham Research Ethics
4
5 336 Committee (REC) as part of gaining Health Research Authority (HRA) approval (17/LO/1975).

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10 338 *Quality Assurance*

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12 339 Monitoring of this study will be to ensure compliance with Good Clinical Practice, and scientific
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14 340 integrity will be managed and oversight retained by the Data Monitoring Committee (DMC) led by Prof
15
16 341 Dominique Michaud. The committee will receive notification every 6 months of the interim and total
17
18 342 accrual. At the discretion of the chair of the DMC, interim analyses may be scheduled as modifications
19
20 343 to the protocol. Additional meetings during the study period may occur at the discretion of the
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22 344 Steering Committee.
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27 346 The study design, analysis and reporting will follow the recent recommendations for good practice in
28
29 347 clinical outcomes assessment by the International Society for Pharmacoeconomics and Outcomes
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31 348 Research (ISPOR) [17].
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36 350 *Data handling*

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39 351 The Chief Investigator and delegates are responsible for daily cohort management. Data quality will
40
41 352 be checked periodically. The following guidelines will be strictly adhered to:

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- 44 • Patient data will be anonymised.
 - 45 • All anonymised data will be stored on a password protected encrypted computer.
 - 46 • All study data will be stored in line with the Data Protection Act as defined in the King's Health
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48 355 Partners' Clinical Trials Office Archiving SOP.
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52 357 The data will be stored as outlined in the data management plan.
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3 3584
5 359 *Insurance/Indemnity*6
7 360 The co-sponsors King's College London and Guy's and St Thomas' NHS Foundation Trust will provide8
9 361 insurance and indemnity.10
11 36212
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14 363 **Discussion**15
16 364 The Graham Roberts study is the first of its kind and thus the first TwiCs study for bladder cancer. It17
18 365 generates a wide variety of research opportunities with limited risk to patients. Participation in19
20 366 research involves some loss of privacy. We will do our best to make sure that all personal21
22 367 information gathered for this study is kept private. As this is a non-interventional prospective cohort23
24 368 study, participation may not have a beneficial effect on patients' bladder cancer prognosis or25
26 369 quality-of-life compared to usual care.27
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30 37031
32 371 The questionnaires to be used are quite detailed and, for the most part, concerns day-to-day33
34 372 activities such as quality and duration of sleep, diet and exercise. The questionnaire does pose some35
36 373 more personal and intrusive questions however, including questions related to symptoms of37
38 374 depression. These questions can be omitted if the participant does not feel comfortable answering39
40 375 them. There is a risk that some participants may be upset by having these questions posed to them.41
42 376 Some participants may prefer to complete the questionnaire themselves, whereas others may prefer43
44 377 to do so with a research assistant. Participants will be fully informed about these potential harms45
46 378 and enabled to make an informed decision regarding participation. We consider that the potential47
48 379 minor harms are outweighed by the potential benefits of the research.49
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52 38053
54 381 Future research using the data in this study could lead to medical and scientific products,55
56 382 discoveries, as well as interventions that improve the prevention, diagnosis and treatment of57
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3 383 bladder cancer. A benefit for the patients is also the possibility to be part of future RCTs by providing
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5 384 consent for being part of the intervention arm.
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10 386 **Trial Status**

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12 387 Protocol Version and Number: Version 2, January 2018

13
14 388 Date of commencement of recruitment: 22nd February 2018

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16 389 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-BI	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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Secondary Subject Heading:	Epidemiology, Oncology, Urology

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

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Manuscripts

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

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3 **32 Abstract**
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5 **33 Introduction:** Given the need for more bladder cancer research and the recently observed
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7 **34** advantages of introducing the trials within cohort (TwICs) design, the set-up of the Graham Roberts
8
9 **35** Study (Roberts Study) will provide valuable infrastructure to answer a wide variety of research
10
11 **36** questions of a clinical, mechanistic, as well as supportive care nature in the area of bladder cancer.
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14 **37 Methods:** Using the TwICs design, we will recruit patients aged 18 or older who are willing and able
15
16 **38** to provide signed informed consent and have a diagnosis of an active new or recurrent bladder
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18 **39** cancer into this prospective cohort study. All patients have to have a basic understanding of the
19
20 **40** English language. The following questionnaires will be collected baseline and every 12 months:
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22 **41** Functional assessment of chronic illness therapy for bladder cancer (FACT-BI), the Functional
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24 **42** assessment of chronic illness therapy-fatigue (FACIT-Fatigue), the Patient health questionnaire-9
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26 **43** (PHQ-9), the Standardised instrument for a generic health status (EQ-5D-5L), a questionnaire to
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28 **44** assess health enhancing physical activity (SQUASH), and the Hertfordshire short questionnaire to
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30 **45** assess diet quality.
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33
34 **46 Ethics and Dissemination:** Due to the nature of this study, we obtained full ethical clearance from
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36 **47** the London - Fulham Research Ethics Committee (17/LO1975). All participants must provide full
37
38 **48** informed consent before recruitment onto the study. The results of this study will be published in
39
40 **49** peer-reviewed journals and data collected as part of the study will be made available to potential
41
42 **50** collaborators on an application basis.
43
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46 **51**
47
48 **52 Keywords:** trials within cohorts, bladder cancer, randomised controlled trial, prospective cohort
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50 **53** study
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58 **Strengths and Limitations**

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

65 **Background**

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

74
75 The design of this bladder cancer cohort study is similar to the Utrecht cohort for Multiple BREast
76 cancer intervention studies and Long-term evaLuAtion (UMBRELLA) (4), which is based on the TwiCs
77 design introduced by Relton et al. at the University of Sheffield in 2010 (5). It is the first TwiCs design
78 study in the area of bladder cancer.

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

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3 83 practice(5). Such shortcomings relate to recruitment, ethics, patient preferences and treatment
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5 84 comparisons. At least six TwiCs studies are currently ongoing in the UK (6).
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10 86 The Roberts Study will serve as a facility for multiple trials and follows the TwiCs design.
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14 88 The main objectives of the Graham Roberts study (Roberts Study) are:

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- 17 • To create a prospective cohort study of well-characterised bladder cancer patients, which
18 provides the opportunity to conduct a variety of observational studies.
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 - 20 • To create the infrastructure for future RCTs that will allow more efficient recruitment using
21 91 patient-centred informed consent
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28 94 **Methods/Design**

29 95 *TwicCs design*

30 96 The TwiCs design can be described as follows: Firstly, a large observational cohort of patients with
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32 97 the condition of interest is recruited and their outcomes regularly measured. Then for each
33
34 98 randomised controlled trial (RCT), information from the cohort is used to identify all eligible
35
36 99 patients. Some eligible patients are randomly selected and offered the trial intervention. The
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38 100 outcomes of these randomly selected patients are then compared with the outcomes of eligible
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40 101 patients not randomly selected, that is, those receiving usual care. This process can be repeated for
41
42 102 further randomised controlled trials (5).
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50 104 The recruitment and regular follow-up of a large cohort of patients are characteristics of longitudinal
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52 105 observational studies. In the TwiCs design, however, all patients in the cohort consent at the outset
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54 106 to provide data to be used to look at the benefits of treatments for the condition of interest. The
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56 107 capacity for multiple RCTs over time using patients from the same cohort is unique to the TwiCs
57
58 108 design. Random selection of some eligible cohort patients, the comparison of their outcomes with
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3 109 the outcomes in eligible patients not randomly selected and the similarity of the patient-centred
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5 110 informed consent approach to real life situations offer solutions to the ethical criticisms of
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7 111 randomised consent designs (5).
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12 113 *The Graham Roberts Study*
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14 114 Patients will be recruited at Guy's and St Thomas' (GSTT) NHS Foundation Trust, London, UK. All

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16 115 patients will be eligible for the study following their first visit for a new or recurrent bladder cancer

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18 116 diagnosis. Patients with limited understanding of the English language and patients under the age of

19
20 117 18 years are ineligible. Since Guy's and St Thomas NHS Foundation Trust is a referral centre, the

21
22 118 Roberts Study will include patients from various secondary and tertiary hospitals located across the

23
24 119 United Kingdom. Each year, approximately 100 eligible patients visit the Urology Centre of GSTT for

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26 120 bladder cancer management.
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32 122 All eligible patients who have already undergone diagnostic investigations and been informed about

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34 123 a (highly likely) bladder cancer will receive detailed written information about the Roberts Study

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36 124 whilst attending the Urology Centre for their initial appointment. They will be scheduled to see a

37
38 125 member of the direct clinical care team and a research nurse/assistant 30 minutes prior to their first

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40 126 appointment with the Consultant (urology or oncology). During this research consultation, the

41
42 127 research nurse/assistant will explain the study in detail and written informed consent will be

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44 128 obtained from those who agree to participate. Such consent will be gained to allow:
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48 129 • Participation in the Graham Robert's Study cohort and longitudinal study;

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50 130 • The participant to be approached to participate in the intervention arm of any future

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52 131 randomised control trial;

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54 132 • The participant to be randomised to the control arm of any future randomised control trial

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56 133 without knowledge of this status.
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3 134 • Collection and storage of participants biological samples, including blood, urine and tissue,
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5 135 within the KHP Bladder Cancer Biobank;
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8 136 • Linkage and use of participants routinely collected clinical data as recorded in electronic
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10 137 patient records.
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14 139 At the time of full informed consent, the patients will also be provided with the study baseline
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16 140 questionnaire and asked to complete this at a convenient time.
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21 142 For those eligible patients who have not yet been informed about their bladder cancer diagnosis at
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23 143 the time of visiting the Urology Centre, detailed written information about the Roberts Study will be
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25 144 provided by a research nurse/assistant after they have met with the consultant. If the patients are
26
27 145 not ready to discuss this study in further detail at this point, a follow-up call will be made one week
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29 146 later to obtain their consent, if they have agreed to participate. Full written informed consent is
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31 147 subsequently obtained at the patients next clinical appointment.
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39 150 Data from all patients may be used for observational studies in the Roberts Study, but only those
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41 151 who provide consent for randomisation are eligible for participation in the RCTs within the Roberts
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43 152 Study.
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48 154 Thus, the TwiCs design is based on an “asymmetric informed consent”. After recruitment into the
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50 155 Roberts cohort, randomisation of eligible subjects, can be followed by an asymmetric treatment of
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52 156 the two arms; those selected for the experimental arm provide informed consent for the
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54 157 intervention trial, while the data from the control arm are used based on prior broad permission.
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57 158 Hence, the cohort participants are informed about future research within the cohort.
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3 160 *Selection and withdrawal of subjects*
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5 161 Patients eligible to participate in this study are those who meet all of the following inclusion criteria:
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- 7 162
- 8 • Appointment for a new or recurrent diagnosis of bladder cancer at Guy's and St Thomas' NHS
9 Foundation Trust
 - 10 163
 - 11 164 • Minimum age of 18 years
 - 12 165 • Basic understanding of English
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19 167 Patients will be identified in multi-disciplinary team meetings or in out-patient clinics by the clinical
20 team, in collaboration with the research nurse. Participants have the right to withdraw from the
21 168 study at any time for any reason. Their routine medical and surgical care will not be affected.
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28 171 *Expected duration of the study and sample size*
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30 172 As this study is an observational prospective cohort study, it is difficult to estimate its duration. We
31 aim to recruit a minimum of 400 patients over a period of 5 years, though there is no limit to the
32 173 number of patients needed for a prospective cohort study. Moreover, over time new research
33 174 opportunities will develop and potential funding may become available to continue recruitment into
34 175 the Roberts Study. Patients will be followed up for life through data linkages with Hospital Episode
35 176 Statistics (HES), the Office for National Statistics (ONS) and electronic patient records.
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43 178 As this is a prospective cohort study, with no specific primary research question, it is not possible to
44 179 perform sample size calculations. However, it is still important to consider recruitment rates and
45 180 response rates to the questionnaires.
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50 181 At the point of submission of this protocol (April 2019), 72 bladder cancer patients had provided full
51 written informed consent for the Graham Robert's Study. Of these 72 patients, 64 had completed
52 182 and returned their baseline questionnaire. At current rates of consent, the authors would expect
53 183 baseline recruitment of 400 bladder cancer patients to be complete by 31st December 2022.
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3 186 *Data collection*
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5 187 Within the Roberts Study, various clinical data will be prospectively collected including
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7 188 demographics, tumour characteristics, treatment and CT and MRI imaging data. Clinical data will be
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9 189 captured from electronic medical records, referral letters and annual reports for Public Health
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12 190 England.
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16 192 Socio-demographic data will include sex, date of birth, age at diagnosis, highest level of education,
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18 193 postal code (to estimate the deprivation index), body mass index (BMI) and WHO performance
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20 194 status.
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25 196 The following tumour characteristics will be collected: TNM stage, grade, tumour diameter, number
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27 197 of tumours, histology and morphological codes and invasiveness.
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32 199 Treatment characteristics comprise data on type and timing of treatment given (e.g. intravesical
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34 200 instillations, systemic chemotherapy, radical cystectomy, radiotherapy or other treatments).
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36 201 Additional detailed data, as reported in surgical notes, will be available for those bladder cancer
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38 202 patients who undergo radical cystectomy. Table 1 illustrates the pre-, peri- and postoperative
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40 203 variables which will be collected for this patient subset.
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45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	<p>Table 1: Data collection for those participants of the Roberts Study undergoing radical cystectomy. Preoperative</p>	<p>TNM stage, weight, height, BMI, American Society of Anesthesiologists (ASA) score, previous pelvic surgery, radiation or neoadjuvant chemotherapy</p>
	<p>Perioperative</p>	<p>Type of surgery, type of lymphadenectomy, type of urinary diversion, blood loss, duration of surgery, accidental organ injury during surgery</p>
	<p>Postoperative</p>	<p>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</p>

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3 206 Information on disease progression, recurrence and survival will be collected annually by means of
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5 207 the data linkages with HES, ONS and electronic patient records. We will also collect patient-reported
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7 208 outcome measures (PROMs) by means of validated questionnaires designed to quantify health-
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9 209 related Quality of Life (QoL) from the patients' perspective. These questionnaires will be given
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11 210 (paper (post) or digital (email or tablet in clinic)) to patients upon entry into the cohort (baseline)
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14 211 and every 12 months thereafter with a total follow-up of at least 10 years. It will take about 30
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16 212 minutes to fill out the set of questionnaires at each time point.
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21 214 PROMs will be collected on QoL, fatigue, anxiety and depression, physical activity, dietary habits as
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23 215 well as risk behaviour in terms of known bladder cancer risk factors. Following an assessment of
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25 216 smoking behaviour, alcohol consumption and occupational bladder cancer risk factors, the following
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27 217 validated questionnaires will be used (see Additional File 1):
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- 30 218
- 31
32 219 • **Quality of Life:** Functional assessment of chronic illness therapy for bladder cancer (FACT-BI
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34 220 (7))
 - 35
36 221 • **Fatigue:** Functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue (8))
 - 37
38 222 • **Depression:** Patient health questionnaire-9 (PHQ-9 (9))
 - 39
40 223 • **Health :** Standardised instrument for use as a measure of health outcome (EQ-5D-5L(10))
 - 41
42 224 • **Physical activity:** Questionnaire to assess health enhancing physical activity (SQUASH (11))
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44 225 • **Assessment of dietary habits:** Short questionnaire to assess diet quality (12)
 - 45
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48 227 *Assessment of safety*
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52 228 As this is a prospective cohort study with no specific interventions, adverse events (AEs) are unlikely
53
54 229 to take place. Nevertheless, if filling out questionnaire data should ever result in an AE, it will be
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56 230 graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
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58 231 and coded. These will be reported to the Data Monitoring Committee.
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3 232 Given that we see on average about 100 eligible patients per year, we expect to recruit at least 400
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5 233 patients over a period of five years. However, as described above, if more research and/or funding
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7 234 opportunities come up, we will continue recruitment into the Roberts study.
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11 236 *Patient and Public Engagement*

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14 237 The development of the Graham Roberts Study was informed in collaboration with patient
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16 238 representatives diagnosed and treated at Guy's and St Thomas' NHS Foundation Trust. Prior to
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18 239 development of the study protocol, a focus group was held to discuss the acceptability of the TwiCs
19
20 240 study design and the content of the self-administered questionnaire. Patients of similar bladder
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22 241 cancer diagnoses to those that will be consented onto the study were recruited into this focus
23
24 242 group. Based on the patient's experiences and preferences, the Graham Roberts Study design was
25
26 243 agreed. Results of the study will be disseminated to the patients through annual newsletters and on
27
28 244 a study specific website for patients.
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32 246 *Direct Access to Source Data and Documents*

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35 247 The Investigator will prepare and maintain adequate and accurate source documents designed to
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37 248 record all observations and other pertinent data for each patient in the Roberts Study. Study
38
39 249 personnel will enter data from source documents corresponding to a patient's visit into the
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41 250 protocol-specific electronic case report forms (CRFs) in a dedicated, secure data warehouse. Patients
42
43 251 will not be identified by name in the study database or on any study documents to be collected by
44
45 252 the Sponsor (or Designee), but will be identified by patient ID numbers.
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51 254 The database will be safeguarded against unauthorised access with established security procedures;
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53 255 nightly backup of the database and related software files will be maintained. At pre-specified
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55 256 junctures of the protocol (e.g., production of interim and final reports), data for analysis will be
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57 257 locked and cleaned as per established procedures.
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5 259 If a correction is required to a CRF, the time and date stamps will track the person entering or
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7 260 updating CRF data and create an electronic audit trail. The Chief Investigator is responsible for
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9 261 reviewing all information collected on patients enrolled in this study for completeness and accuracy.
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14 263 To enable evaluations and/or audits from regulatory authorities, the CI agrees to keep records,
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16 264 including the identity of all participating subjects (sufficient information to link records, e.g. CRFs
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18 265 and hospital records), all original signed informed consent forms, safety reporting forms, source
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20 266 documents and detailed records of treatment disposition and adequate documentation of relevant
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22 267 correspondence (e.g. letters, meeting minutes, telephone call reports). The records should be
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24 268 retained by the CI according to the International Conference on Harmonisation (ICH) or local
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26 269 regulations; all study documentation must be retained for 10 years after the study ends.
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32 271 *Quality Assurance*

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34 272 Monitoring of this study will be to ensure compliance with Good Clinical Practice, and scientific
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36 273 integrity will be managed and oversight retained by the Data Monitoring Committee (DMC) led by Prof
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38 274 Dominique Michaud. The committee will receive notification every 6 months of the interim and total
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40 275 accrual. At the discretion of the chair of the DMC, interim analyses may be scheduled as modifications
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42 276 to the protocol. Additional meetings during the study period may occur at the discretion of the
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44 277 Steering Committee.
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50 279 The study design, analysis and reporting will follow the recent recommendations for good practice in
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52 280 clinical outcomes assessment by the International Society for Pharmacoeconomics and Outcomes
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54 281 Research (ISPOR) (13).
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3 283 *Data handling*
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5 284 The Chief Investigator and delegates are responsible for daily cohort management. Data quality will
6
7 285 be checked periodically. The following guidelines will be strictly adhered to:

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 - 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
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289 Partners' Clinical Trials Office Archiving SOP.
290 The data will be stored as outlined in the data management plan.

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292 *Insurance/Indemnity*

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

295

296 **Discussion**

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

303

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

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3 309 Some participants may prefer to complete the questionnaire themselves, whereas others may prefer
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5 310 to do so with a research assistant. Participants will be fully informed about these potential harms
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7 311 and enabled to make an informed decision regarding participation. We consider that the potential
8
9 312 minor harms are outweighed by the potential benefits of the research.
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14 314 Future research using the data in this study could lead to medical and scientific products,
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16 315 discoveries, as well as interventions that improve the prevention, diagnosis and treatment of
17
18 316 bladder cancer. A benefit for the patients is also the possibility to be part of future RCTs by providing
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20 317 consent for being part of the intervention arm.
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23 318

24 319 **Trial Status**

25
26 320 Protocol Version and Number: Version 2, January 2018

27
28 321 Date of commencement of recruitment: 22nd February 2018

29
30 322 Projected date of recruitment completion: 28th October 2022
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32 323

33 324 **Ethics and Dissemination**

34
35 325 The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996),
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37 326 the principles of GCP, and in accordance with all applicable regulatory requirements including but
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39 327 not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial)
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41 328 Regulations 2004, as amended in 2006 and any subsequent amendments. This protocol and related
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43 329 documents were approved by the London – Fulham Research Ethics Committee (REC) as part of
44
45 330 gaining Health Research Authority (HRA) approval (17/LO/1975).
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50 332 After completion of an RCT within the Roberts Study, all patients – irrespective of participation in the
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52 333 specific study – will receive aggregated results via a newsletter that they can subscribe to at time of
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334 initial consent. All results associated with this study will be published in journals as peer-reviewed
335 articles.

For peer review only

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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-BI	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
TriCs	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

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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

1
2 **[Women only]** The next group of questions are about your reproductive history. Firstly,
3 how old were you when you had your first menstrual period?
4

5 years old
6

- 7 I prefer not to answer
8 I don't know
9

10 Have you had at least one menstrual period in the past 12 months?
11

- 12 Yes
13 No
14 I prefer not to answer
15 I don't know
16

17 Are you pregnant or breastfeeding?
18

- 19 Yes
20 No
21 I prefer not to answer
22 I don't know
23

24 Have you had surgery to remove your uterus (hysterectomy)?
25

- 26 Yes
27 No
28 I prefer not to answer
29 I don't know
30

31 Have you had any of your ovaries surgically removed (oophorectomy)?
32

- 33 Yes
34 No
35 I prefer not to answer
36 I don't know
37

38 How many of your ovaries were removed?
39

- 40 One
41 Both
42 I prefer not to answer
43 I don't know
44

45 Have you ever taken birth control pills?
46

- 47 Yes
48 No
49 I prefer not to answer
50 I don't know
51

52 At what age did you first start taking birth control pills?
53

54 _____ year old
55 I prefer not to answer
56 I don't know
57

58 How long did you take birth control pills?
59

60 _____ years _____ months
 I prefer not to answer
 I don't know

1 How many times have you been pregnant?

- 2 Never
- 3 _____ times
- 4 I prefer not to answer
- 5 I don't know
- 6
- 7

8 How many of your pregnancies ended in a live birth?

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- 10 _____
- 11 I prefer not to answer
- 12 I don't know
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Section 2 – History of tobacco consumption**Please tick the most appropriate answer:**

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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, Altacor)	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?**

Currently smoke?	Cigarettes		Pipe		Cigars	
	YES	NO	YES	NO	YES	NO
If yes, how many per day?	1-4		1-4		1-4	
	5-14		5-10		5-10	
	15-24		10 or more		10 or more	
	25-34					
	35-44					
	45 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	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
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.

<u>ADDITIONAL CONCERNS</u>		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 <u>starting</u> things because I am tired.....	0	1	2	3	4
An4	I have trouble <u>finishing</u> 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

Peer review only

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

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

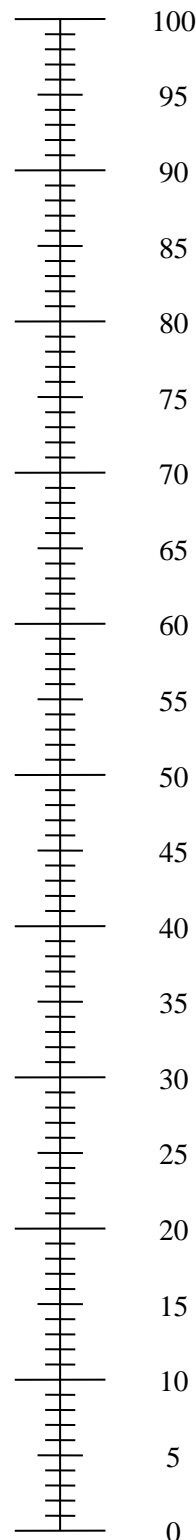
PAIN / DISCOMFORT

- 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

The best health
you can imagine



The worst health
you can imagine

- 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 do 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? _____

BMJ Open

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

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Epidemiology, Oncology, Urology, Research methods

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

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Manuscripts

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

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2
3 **32 Abstract**
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5 **33 Introduction:** Given the need for more bladder cancer research and the recently observed
6
7 **34** advantages of introducing the trials within cohort (TwICs) design, the set-up of the Graham Roberts
8
9 **35** Study (Roberts Study) will provide valuable infrastructure to answer a wide variety of research
10
11
12 **36** questions of a clinical, mechanistic, as well as supportive care nature in the area of bladder cancer.
13

14 **37 Methods:** Using the TwICs design, we will recruit patients aged 18 or older who are willing and able
15
16
17 **38** to provide signed informed consent and have a diagnosis of new or recurrent bladder cancer into
18
19 **39** this prospective cohort study. All patients must have a basic understanding of the English language.
20

21 **40** The following questionnaires will be collected at baseline and every 12 months subsequently:
22

23 **41** Functional assessment of chronic illness therapy for bladder cancer (FACT-BI), the Functional
24
25 **42** assessment of chronic illness therapy-fatigue (FACIT-Fatigue), the Patient Health questionnaire-9
26
27 **43** (PHQ-9), the Standardised instrument for a generic health status (EQ-5D-5L), a questionnaire to
28
29 **44** assess health enhancing physical activity (SQUASH), and the Hertfordshire short questionnaire to
30
31 **45** assess diet quality.
32
33

34 **46 Ethics and Dissemination:** Due to the nature of this study, we obtained full ethical clearance from
35
36
37 **47** the London - Fulham Research Ethics Committee (17/LO1975). All participants must provide full
38
39 **48** informed consent before recruitment onto the study. The results of this study will be published in
40
41 **49** peer-reviewed journals and data collected as part of the study will be made available to potential
42
43 **50** collaborators on an application basis.
44
45

46 **51**

47
48 **52 Keywords:** trials within cohorts, bladder cancer, randomised controlled trial, prospective cohort
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50 **53** study
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58 **Strengths and Limitations**

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

64 **Background**

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

73
74 The design of this bladder cancer cohort study is similar to the Utrecht cohort for Multiple BREast
75 cancer intervention studies and Long-term evaluation (UMBRELLA) (4), which is based on the TwICs
76 design introduced by Relton et al. at the University of Sheffield in 2010 (5). It is the first TwICs design
77 study in the area of bladder cancer.

78
79 The use of TwICs has grown substantially in the last few years, with several new initiatives in the UK.
80 TwICs, originally introduced as cohort multiple randomised controlled trial design, was introduced to
81 address the problems associated with existing approaches for trials informing routine clinical
82 practice(5). Such shortcomings relate to recruitment, ethics, patient preferences and treatment
83 comparisons. At least six TwICs studies are currently ongoing in the UK (6).

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2
3 84
45 85 The Roberts Study will serve as a facility for multiple trials and follows the TwiCs design.
6
78 86
910 87 The main objectives of the Graham Roberts study (Roberts Study) are:
1112 88 • To create a prospective cohort study of well-characterised bladder cancer patients, which
13 provides the opportunity to conduct a variety of observational studies.
14 8915 90 • To create the infrastructure for future RCTs that will allow more efficient recruitment using
16 patient-centred informed consent
17 91
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21
2223 93 **Methods/Design**24 94 *TwiCs design*25
26 95 The TwiCs design can be described as follows: Firstly, a large observational cohort of patients with
27
28 96 the condition of interest is recruited and their outcomes regularly measured. Then for each
29
30 97 randomised controlled trial (RCT), information from the cohort is used to identify all eligible
31
32 98 patients. Some eligible patients are randomly selected and offered the trial intervention. The
33
34 99 outcomes of these randomly selected patients are then compared with the outcomes of eligible
35
36 100 patients not randomly selected, that is, those receiving usual care. This process can be repeated for
37
38 101 further randomised controlled trials (5).
39
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44
4546 103 The recruitment and regular follow-up of a large cohort of patients are characteristics of longitudinal
47
48 104 observational studies. In the TwiCs design, however, all patients in the cohort consent at the outset
49
50 105 to provide data to be used to look at the benefits of treatments for the condition of interest. The
51
52 106 capacity for multiple RCTs over time using patients from the same cohort is unique to the TwiCs
53
54 107 design. Random selection of some eligible cohort patients, the comparison of their outcomes with
55
56 108 the outcomes in eligible patients not randomly selected and the similarity of the patient-centred
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2
3 109 informed consent approach to real life situations offer solutions to the ethical criticisms of
4
5 110 randomised consent designs (5).

6
7 111

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10 112 *The Graham Roberts Study*

11
12 113 Patients will be recruited at Guy's and St Thomas' (GSTT) NHS Foundation Trust, London, UK. All

13
14 114 patients will be eligible for the study following their first visit for a new or recurrent bladder cancer

15
16 115 diagnosis. Patients with limited understanding of the English language and patients under the age of

17
18 116 18 years are ineligible. Since Guy's and St Thomas NHS Foundation Trust is a referral centre, the

19
20 117 Roberts Study will include patients from various secondary and tertiary hospitals located across the

21
22 118 United Kingdom. Each year, approximately 100 eligible patients visit the Urology Centre of GSTT for

23
24 119 bladder cancer management.

25
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28 120

29
30 121 All eligible patients who have already undergone diagnostic investigations and been informed about

31
32 122 a (highly likely) bladder cancer will receive detailed written information about the Roberts Study

33
34 123 whilst attending the Urology Centre for their initial appointment. They will be scheduled to see a

35
36 124 member of the direct clinical care team and a research nurse/assistant 30 minutes prior to their first

37
38 125 appointment with the Consultant (urology or oncology). During this research consultation, the

39
40 126 research nurse/assistant will explain the study in detail and written informed consent will be

41
42 127 obtained from those who agree to participate. Such consent will be gained to allow:

43
44
45 128 • Participation in the Graham Roberts Study cohort and longitudinal study;

46
47 129 • The participant to be approached to participate in the intervention arm of any future

48
49 130 randomised control trial;

50
51 131 • The participant to be randomised to the control arm of any future randomised control trial

52
53 132 without knowledge of this status.

54
55 133 • Collection and storage of participants biological samples, including blood, urine and tissue,

56
57 134 within the KHP Bladder Cancer Biobank;

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- 1
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3 135 • Linkage and use of participants routinely collected clinical data as recorded in electronic
4
5 136 patient records.
6
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9
10 138 At the time of full informed consent, the patients will also be provided with the study baseline
11
12 139 questionnaire and asked to complete this at a convenient time.
13

14 140

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16 141 For those eligible patients who have not yet been informed about their bladder cancer diagnosis at
17
18 142 the time of visiting the Urology Centre, detailed written information about the Roberts Study will be
19
20 143 provided by a research nurse/assistant after they have met with the consultant. If the patients are
21
22 144 not ready to discuss this study in further detail at this point, a follow-up call will be made one week
23
24 145 later to obtain their consent, if they have agreed to participate. Full written informed consent is
25
26 146 subsequently obtained at the patients next clinical appointment.
27

28 147

29
30 148 Data from all patients may be used for observational studies in the Roberts Study, but only those
31
32 149 who provide consent for randomisation are eligible for participation in the RCTs within the Roberts
33
34 150 Study.
35

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39 152 Thus, the TwiCs design is based on an “asymmetric informed consent”. After recruitment into the
40
41 153 Roberts cohort, randomisation of eligible subjects, can be followed by an asymmetric treatment of
42
43 154 the two arms; those selected for the experimental arm provide informed consent for the
44
45 155 intervention trial, while the data from the control arm are used based on prior broad permission.
46
47 156 Hence, the cohort participants are informed about future research within the cohort.
48
49 157

50 158

51 159

52 158 *Selection and withdrawal of subjects*

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54
55 159 Patients eligible to participate in this study are those who meet all of the following inclusion criteria:
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3 160 • Appointment for a new or recurrent diagnosis of bladder cancer at Guy's and St Thomas' NHS
4
5 161 Foundation Trust

6
7
8 162 • Minimum age of 18 years

9
10 163 • Basic understanding of English

11
12 164

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14 165 Patients will be identified in multi-disciplinary team meetings or in out-patient clinics by the clinical
15
16 166 team, in collaboration with the research nurse. Participants have the right to withdraw from the
17
18 167 study at any time for any reason. Their routine medical and surgical care will not be affected.
19
20

21 168

22
23 169 *Expected duration of the study and sample size*

24
25 170 As this study is an observational prospective cohort study, it is difficult to estimate its duration. We
26
27 171 aim to recruit a minimum of 400 patients over a period of 5 years, though there is no limit to the
28
29 172 number of patients needed for a prospective cohort study. Moreover, over time new research
30
31 173 opportunities will develop and potential funding may become available to continue recruitment into
32
33 174 the Roberts Study. Patients will be followed up for life through data linkages with Hospital Episode
34
35 175 Statistics (HES), the Office for National Statistics (ONS) and electronic patient records.
36
37

38
39 176 As this is a prospective cohort study, with no specific primary research question, it is not possible to
40
41 177 perform sample size calculations. However, it is still important to consider recruitment rates and
42
43 178 response rates to the questionnaires.
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47
48 180 Recruitment to the Graham Roberts Study commenced on 23rd March 2018. At the point of
49
50 181 submission of this protocol (April 2019), 84 bladder cancer patients had been approached with a
51
52 182 patient information sheet, and 72 patients had provided full written informed consent and
53
54 183 completed the baseline study questionnaire. At current rates of consent, the authors project the
55
56 184 baseline recruitment of 400 bladder cancer patients to be complete by 31st August 2023. It is
57
58 185 expected, however, that recruitment rates will increase as the direct clinical care team and research
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3 186 nurses/assistants become more efficient at identifying and approaching eligible patients. The
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5 187 projected end of recruitment date is therefore set at 31st December 2022. Moreover, ethical
6
7 188 clearance is in place to recruit until this date.
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11
12 190 *Data collection*

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14 191 Within the Roberts Study, various clinical data will be prospectively collected including
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16 192 demographics, tumour characteristics, treatment and CT and MRI imaging data. Clinical data will be
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18 193 captured from electronic medical records, referral letters and annual reports for Public Health
19
20 194 England.
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25 196 Socio-demographic data will include sex, date of birth, age at diagnosis, highest level of education,
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27 197 postal code (to estimate the deprivation index), body mass index (BMI) and WHO performance
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29 198 status.
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34 200 The following tumour characteristics will be collected: TNM stage, grade, tumour diameter, number
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36 201 of tumours, histology and morphological codes and invasiveness.
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41 203 Treatment characteristics comprise data on type and timing of treatment given (e.g. intravesical
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43 204 instillations, systemic chemotherapy, radical cystectomy, radiotherapy or other treatments).
44

45 205 Additional detailed data, as reported in surgical notes, will be available for those bladder cancer
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47 206 patients who undergo radical cystectomy. Table 1 illustrates the pre-, peri- and postoperative
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49 207 variables which will be collected for this patient subset.
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212 **Table 1:** Data collection for those participants of the Roberts Study undergoing radical
 213 cystectomy

214 .Preoperative	TNM stage, weight, height, BMI, American Society of Anesthesiologists (ASA) score, previous pelvic surgery, radiation or neoadjuvant chemotherapy
215 Perioperative	Type of surgery, type of lymphadenectomy, type of urinary diversion, blood loss, duration of surgery, accidental organ injury during surgery
216 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

217

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

225

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

230

- 231 • **Quality of Life:** Functional assessment of chronic illness therapy for bladder cancer (FACT-BI
 232 (7))
- 233 • **Fatigue:** Functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue (8))
- 234 • **Depression:** Patient health questionnaire-9 (PHQ-9 (9))
- 235 • **Health :** Standardised instrument for use as a measure of health outcome (EQ-5D-5L(10))
- 236 • **Physical activity:** Questionnaire to assess health enhancing physical activity (SQUASH (11))

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3 234 • **Assessment of dietary habits:** Short questionnaire to assess diet quality (12)
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7
8 236 *Assessment of safety*
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10 237 As this is a prospective cohort study with no specific interventions, adverse events (AEs) are unlikely
11
12 238 to take place. Nevertheless, if filling out questionnaire data should ever result in an AE, it will be
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14 239 graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
15
16 240 and coded. These will be reported to the Data Monitoring Committee.

17
18 241 Given that we see on average about 100 eligible patients per year, we expect to recruit at least 400
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20 242 patients over a period of five years. However, as described above, if more research and/or funding
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22 243 opportunities come up, we will continue recruitment into the Roberts study.
23
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28 245 *Patient and Public Engagement*
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30 246 The development of the Graham Roberts Study was informed in collaboration with patient
31
32 247 representatives diagnosed and treated at Guy's and St Thomas' NHS Foundation Trust. Prior to
33
34 248 development of the study protocol, a focus group was held to discuss the acceptability of the TwiCs
35
36 249 study design and the content of the self-administered questionnaire. Patients of similar bladder
37
38 250 cancer diagnoses to those that will be consented onto the study were recruited into this focus
39
40 251 group. Based on the patient's experiences and preferences, the Graham Roberts Study design was
41
42 252 agreed. Results of the study will be disseminated to the patients through annual newsletters and on
43
44 253 a study specific website for patients.
45
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49
50 255 *Direct Access to Source Data and Documents*
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52 256 The Investigator will prepare and maintain adequate and accurate source documents designed to
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54 257 record all observations and other pertinent data for each patient in the Roberts Study. Study
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56 258 personnel will enter data from source documents corresponding to a patient's visit into the
57
58 259 protocol-specific electronic case report forms (CRFs) in a dedicated, secure data warehouse. Patients
59
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3 260 will not be identified by name in the study database or on any study documents to be collected by
4
5 261 the Sponsor (or Designee), but will be identified by patient ID numbers.
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10 263 The database will be safeguarded against unauthorised access with established security procedures;
11
12 264 nightly backup of the database and related software files will be maintained. At pre-specified
13
14 265 junctures of the protocol (e.g., production of interim and final reports), data for analysis will be
15
16 266 locked and cleaned as per established procedures.
17
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20
21 268 If a correction is required to a CRF, the time and date stamps will track the person entering or
22
23 269 updating CRF data and create an electronic audit trail. The Chief Investigator is responsible for
24
25 270 reviewing all information collected on patients enrolled in this study for completeness and accuracy.
26
27

28 271
29
30 272 To enable evaluations and/or audits from regulatory authorities, the CI agrees to keep records,
31
32 273 including the identity of all participating subjects (sufficient information to link records, e.g. CRFs
33
34 274 and hospital records), all original signed informed consent forms, safety reporting forms, source
35
36 275 documents and detailed records of treatment disposition and adequate documentation of relevant
37
38 276 correspondence (e.g. letters, meeting minutes, telephone call reports). The records should be
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40 277 retained by the CI according to the International Conference on Harmonisation (ICH) or local
41
42 278 regulations; all study documentation must be retained for 10 years after the study ends.
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47 280 *Quality Assurance*

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50 281 Monitoring of this study will be performed to ensure compliance with Good Clinical Practice, and
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52 282 scientific integrity will be managed and oversight retained by the Data Monitoring Committee (DMC)
53
54 283 led by Prof Dominique Michaud. The committee will receive notification every 6 months of the
55
56 284 interim and total accrual. At the discretion of the chair of the DMC, interim analyses may be
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3 285 scheduled as modifications to the protocol. Additional meetings during the study period may occur
4
5 286 at the discretion of the Steering Committee.
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10 288 The study design, analysis and reporting will follow the recent recommendations for good practice in
11
12 289 clinical outcomes assessment by the International Society for Pharmacoeconomics and Outcomes
13
14 290 Research (ISPOR) (13).
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17 291

18 292 *Data handling*

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20
21 293 The Chief Investigator and delegates are responsible for daily cohort management. Data quality will
22
23 294 be checked periodically. The following guidelines will be strictly adhered to:

- 25 295 • Patient data will be anonymised.
- 26
27
28 296 • All anonymised data will be stored on a password protected encrypted computer.
- 29
30 297 • All study data will be stored in line with the Data Protection Act as defined in the King's
31
32 298 Health Partners' Clinical Trials Office Archiving SOP.

33
34 299 The data will be stored as outlined in the data management plan.
35
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37 300

38 39 301 *Insurance/Indemnity*

40
41 302 The co-sponsors King's College London and Guy's and St Thomas' NHS Foundation Trust will provide
42
43 303 insurance and indemnity.
44
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46 304

47 48 305 **Discussion**

49
50 306 The Graham Roberts study is the first of its kind and thus the first TwiCs study for bladder cancer. It
51
52 307 generates a wide variety of research opportunities with limited risk to patients. Participation in
53
54 308 research involves some loss of privacy. We will do our best to make sure that all personal
55
56
57 309 information gathered for this study is kept private. As this is a non-interventional prospective cohort
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1
2
3 310 study, participation may not have a beneficial effect on patients' bladder cancer prognosis or
4
5 311 quality-of-life compared to usual care.
6
7 312
8
9 313 The questionnaires to be used are quite detailed and, for the most part, concerns day-to-day
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11 314 activities such as quality and duration of sleep, diet and exercise. The questionnaire does pose some
12
13 315 more personal and intrusive questions however, including questions related to symptoms of
14
15 316 depression. These questions can be omitted if the participant does not feel comfortable answering
16
17 317 them. There is a risk that some participants may be upset by having these questions posed to them.
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19 318 Some participants may prefer to complete the questionnaire themselves, whereas others may prefer
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21 319 to do so with a research assistant. Participants will be fully informed about these potential harms
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23 320 and enabled to make an informed decision regarding participation. We consider that the potential
24
25 321 minor harms are outweighed by the potential benefits of the research.
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27 322
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29 323 Future research using the data in this study could lead to medical and scientific products,
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31 324 discoveries, as well as interventions that improve the prevention, diagnosis and treatment of
32
33 325 bladder cancer. A benefit for the patients is also the possibility to be part of future RCTs by providing
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35 326 consent for being part of the intervention arm.
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43 328 **Trial Status**

44
45 329 Protocol Version and Number: Version 2, January 2018
46
47 330 Date of commencement of recruitment: 23rd March 2018
48
49 331 Projected date of recruitment completion: 31st December 2022
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51

52 332

53 333 **Ethics and Dissemination**

54
55 334 The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996),
56
57 335 the principles of GCP, and in accordance with all applicable regulatory requirements including but
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2
3 336 not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial)
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5 337 Regulations 2004, as amended in 2006 and any subsequent amendments. This protocol and related
6
7 338 documents were approved by the London – Fulham Research Ethics Committee (REC) as part of
8
9
10 339 gaining Health Research Authority (HRA) approval (17/LO/1975).
11

12 340

14 341 After completion of an RCT within the Roberts Study, all patients – irrespective of participation in the
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16 342 specific study – will receive aggregated results via a newsletter that they can subscribe to at time of
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18 343 initial consent. All results associated with this study will be published in journals as peer-reviewed
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21 344 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-BI	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

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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

1
2 **[Women only]** The next group of questions are about your reproductive history. Firstly,
3 how old were you when you had your first menstrual period?
4

5 years old
6

- 7 I prefer not to answer
8 I don't know
9

10 Have you had at least one menstrual period in the past 12 months?
11

- 12 Yes
13 No
14 I prefer not to answer
15 I don't know
16

17 Are you pregnant or breastfeeding?
18

- 19 Yes
20 No
21 I prefer not to answer
22 I don't know
23

24 Have you had surgery to remove your uterus (hysterectomy)?
25

- 26 Yes
27 No
28 I prefer not to answer
29 I don't know
30

31 Have you had any of your ovaries surgically removed (oophorectomy)?
32

- 33 Yes
34 No
35 I prefer not to answer
36 I don't know
37

38 How many of your ovaries were removed?
39

- 40 One
41 Both
42 I prefer not to answer
43 I don't know
44

45 Have you ever taken birth control pills?
46

- 47 Yes
48 No
49 I prefer not to answer
50 I don't know
51

52 At what age did you first start taking birth control pills?
53

54 _____ year old
55 I prefer not to answer
56 I don't know
57

58 How long did you take birth control pills?
59

60 _____ years _____ months
 I prefer not to answer
 I don't know

1 How many times have you been pregnant?

- 2 Never
- 3 _____ times
- 4 I prefer not to answer
- 5 I don't know
- 6
- 7

8 How many of your pregnancies ended in a live birth?

9

- 10 _____
- 11 I prefer not to answer
- 12 I don't know
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Section 2 – History of tobacco consumption**Please tick the most appropriate answer:**

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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

1
2 **8. How old were you when you first started smoking at least one cigar per week?**

3 _____ years old

- 4 I refuse to answer
5 I don't know
6

7
8 **9. How old were you when you last smoked cigars?**

9 _____ years old

- 10 I still smoke cigars
11 I refuse to answer
12 I don't know
13

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

16 _____ years _____ months

- 17 I don't know
18 I prefer not to answer
19

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

22 Less than one

23 _____

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

- 25 More than 95
26 I refuse to answer
27 I don't know
28
29

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

- 32 Yes
33 No
34 I prefer not to answer
35 I don't know
36
37

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

40 _____ years old

- 41 I refuse to answer
42 I don't know
43

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

45 _____ years old

- 46 I still smoke a pipe
47 I refuse to answer
48 I don't know
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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, Altacor)	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?**

Currently smoke?	Cigarettes		Pipe		Cigars	
	YES	NO	YES	NO	YES	NO
If yes, how many per day?	1-4		1-4		1-4	
	5-14		5-10		5-10	
	15-24		10 or more		10 or more	
	25-34					
	35-44					
	45 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	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
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.

<u>ADDITIONAL CONCERNS</u>		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 <u>starting</u> things because I am tired.....	0	1	2	3	4
An4	I have trouble <u>finishing</u> 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

Peer review only

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

- 1 I have no problems in walking about
- 2
- 3 I have slight problems in walking about
- 4
- 5 I have moderate problems in walking about
- 6
- 7 I have severe problems in walking about
- 8
- 9 I am unable to walk about

SELF-CARE

- 10 I have no problems washing or dressing myself
- 11
- 12 I have slight problems washing or dressing myself
- 13
- 14 I have moderate problems washing or dressing myself
- 15
- 16 I have severe problems washing or dressing myself
- 17
- 18 I am unable to wash or dress myself

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

- 19 I have no problems doing my usual activities
- 20
- 21 I have slight problems doing my usual activities
- 22
- 23 I have moderate problems doing my usual activities
- 24
- 25 I have severe problems doing my usual activities
- 26
- 27 I am unable to do my usual activities

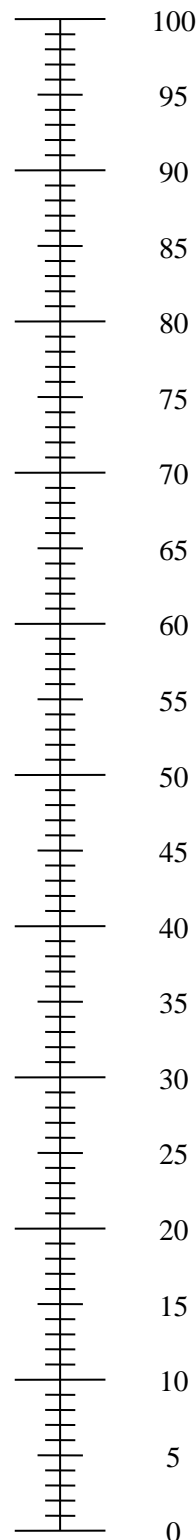
PAIN / DISCOMFORT

- 28 I have no pain or discomfort
- 29
- 30 I have slight pain or discomfort
- 31
- 32 I have moderate pain or discomfort
- 33
- 34 I have severe pain or discomfort
- 35
- 36 I have extreme pain or discomfort

ANXIETY / DEPRESSION

- 37 I am not anxious or depressed
- 38
- 39 I am slightly anxious or depressed
- 40
- 41 I am moderately anxious or depressed
- 42
- 43 I am severely anxious or depressed
- 44
- 45 I am extremely anxious or depressed

The best health
you can imagine



- 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 =

The worst health
you can imagine

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 do 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? _____