Designing a Pragmatic Intervention to Help Improve the Bladder Cancer Patient Experience

Agustina Bessa1, Cecilia Bosco1, Fidelma Cahill1, Beth Russell1, Louis Fox1, Charlotte Moss1, Harriet Wylie1, Anna Haire1, Saran Green1, Deborah Enting1,2, Shamim Khan2, Rajesh Nair2, Ramesh Thurairaja2, Kathryn Chatterton2, Suzanne Amery2, Nicola Peat2, Sue Smith2, Stuart Spear2, Richard T Bryan3, Leila Frodsham2, Danny Burke2, Jeannie Rigby4, Lydia Makaroff4, Phil Kelly4, Melanie Costin5, Christel Häggström6,7, and Mieke Van Hemelrijck1

Abstract
Bladder cancer (BC) is the 10th most common malignancy worldwide and yet the patient experience is found to be worse than that of patients diagnosed with other cancer types. We aimed to develop a wellbeing intervention to help improve the bladder cancer patient experience by ameliorating their health-related Quality of Life (HRQoL). We followed the 3 phases of the modified Medical Research Council (MRC) Framework for development of complex interventions. Following a systematic review of the literature on mental, sexual, and physical wellbeing, we conducted discussion groups with patients and healthcare professionals on these 3 themes. A consultation phase was then conducted with all relevant stakeholders to co-design a wellbeing intervention as part of a feasibility study. A pragmatic wellbeing feasibility trial was designed based on the hypothesis that a wellbeing program will increase patient awareness and attendance to services available to them and will better support their needs to improve HRQoL. The primary feasibility endpoints are patient attendance to the services offered and changes in HRQoL. The principle of patient centered care has strengthened the commitment to provide a holistic approach to support BC patients. In this study, we developed a wellbeing intervention in collaboration with patients and healthcare professionals to meet an unmet need in terms of the BC patient experience.

Keywords
bladder cancer, wellbeing intervention, quality of life, patient experience, patient wellbeing

What do we already know about this topic?
Bladder cancer is the 10th most common malignancy worldwide and yet there is evidence that the patient experience for people with BC is worse than that for patients diagnosed with other cancers. HRQoL issues are thus a major component of the BC patient experience because of the disease and treatment-specific effects on functional outcomes, body image, mental and sexual wellbeing, and social interactions. Therefore, wellbeing programs need to be developed to support BC patients.

How does your research contribute to the field?
While awareness of the importance of wellbeing for BC survivors is growing, several literature reviews (highlighted below) indicate that further studies are needed to assess the role of interventions to support treatments, improve patient experience, and consequently HRQoL.

What are your research’s implications toward theory, practice, or policy?
This study provides an example of how the modified MRC framework can be used to develop a holistic and pragmatic approach to incorporate in different hospital settings with the aim to support BC patients without overloading the healthcare system. It is an example of how cross-collaboration with patients, healthcare professionals, and Action Bladder Cancer UK and Fight Bladder Cancer within the modified MRC framework adds on the quality and value of the complex intervention designed.
Background

Bladder cancer (BC) is the 10th most common malignancy worldwide and yet there is evidence that the patient experience for people with BC is worse than that for patients diagnosed with other cancers.1 From diagnosis to death, it is one of the most expensive cancers to treat on a per patient basis.2 Due to chronic lack of research funding internationally, no substantial change in survival outcomes for >30 years has been reported.2,3 No patient stratification according to the molecular characteristics of individual tumors is yet available, which results in a risk of over- or under-treatment. Current methods of diagnosis, treatment, and monitoring are invasive and lifelong. However, whilst the causes of the poor patient experience are multifactorial, effects on health-related quality of life (HRQoL) provide opportunities for interventions to be offered that support the needs of BC patients.1

The World Health Organization (WHO) defines HRQoL as an individual’s perception of their position in life, within the context of their culture and value system and in relation to their goals, expectations, standards, and concerns.4 A related concept of HRQoL is well-being, which assesses the positive aspects of a person’s life, such as positive emotions and life satisfaction.5 In addition, it is interesting to note that the definitions of mental and sexual health, as defined by the WHO,6 clearly overlap with the definition of HRQoL. It is also well stated by the WHO that physical activity plays an important role in reducing the risk of cancer and depression.6

HRQoL issues are thus a major component of the BC patient experience because of the disease and treatment-specific effects on functional outcomes, body image, mental and sexual wellbeing, and social interactions. Although this impact of a BC diagnosis on the mental,7 sexual,8 and physical wellbeing is well recognized, existing targeted interventions are still very limited.9 Hence, there is an urgent need to develop personalized intervention(s) to improve the mental, sexual, and physical wellbeing of BC patients. Here, we report on the process for the development of such interventions using a modified Medical Research Council (MRC) Framework for developing complex interventions,10 as to allow other institutions to also benefit from this pragmatic approach to improve the BC patient experience.

Methods

Following a modified version of the MRC framework for developing complex interventions,10 we designed a feasibility trial that can be integrated easily into standard care with the overall aims of improving the mental, sexual, and physical wellbeing of BC patients. We used the following 3-phased approach: (1) identifying the relevant existing evidence, (2) consultation phase through discussion groups, and (3) development of a feasibility trial (Figure 1).

Phase 1

Three systematic reviews were conducted following the PRISMA guidelines11 to specifically address the following 3 questions for BC patients:

1. What mental wellbeing interventions are the most beneficial?
2. What are the needs of patients regarding sexual wellbeing?
3. Is there a need for exercise interventions in the patient pathway?

Details on methodology have been reported elsewhere.12–15

Phase 2

To further understand how the BC patient experience can be ameliorated through improvements in HRQoL, we needed to identify the required changes in the current standard of care, and explore optimal approaches to delivering these changes. We therefore aimed to develop an understanding of wellbeing interventions (their structures, content, and timing) through several discussion groups with patients, their carers, and healthcare professionals. These discussion groups were based on topic guides developed from the information obtained in phase 1. Further details on the conduct of these discussion groups are reported elsewhere.16

1King’s College London, London, UK
2Guy’s and St Thomas’ NHS Foundation Trust, London, UK
3University of Birmingham, Birmingham, UK
4Action Bladder Cancer, Gloucestershire, UK
5Fight Bladder Cancer, Oxfordshire, UK
6Uppsala University, Uppsala, Sweden
7Umeå University, Umeå, Sweden

Received 15 February 2021; revised 29 April 2021; revised manuscript accepted 7 June 2021

Corresponding Author:
Agustina Bessa, Translational Oncology & Urology Research, School of Cancer and Pharmaceutical Studies, King’s College London, Guy’s Hospital, 3rd Floor, Bermondsey Wing, London SE1 9RT, UK.
Email: agustina.m.bessa@gmail.com
Phase 3

A consultation with all stakeholders (patients, healthcare professionals, and the patient support groups Action Bladder Cancer UK and Fight Bladder Cancer) was undertaken to incorporate the findings from phase 1 and phase 2 into a feasibility trial. More specifically, this consultation phase included a clinical oncologist, a medical oncologist, a urological surgeon, 3 nurse specialists, a physiotherapist, a patient, and public involvement specialist, and 3 patients (1 male and 2 female) to discuss the following points:

1. What would be a pragmatic wellbeing intervention for BC patients with the aim of improving sexual, mental, and/or physical wellbeing?
2. What specific information needs to be provided, for which patient groups, and who can implement such a wellbeing intervention?
3. What would be the best approach to deliver/implement the intervention into the current standard of care?
4. How should the feasibility of a wellbeing intervention be assessed?

Results

Phase 1

Phase 1 of the modified MRC framework resulted in 3 published literature reviews. In the mental wellbeing literature review, no mental wellbeing interventions specifically designed for BC patients were identified, and so our systematic review for this topic was extended to assess mental wellbeing interventions for all urological cancer types—with a specific focus on reported endpoints as well as the structure and type of the interventions. In this literature review we found that couple base interventions provided the best results, and depression was the most commonly reported endpoint.

Regarding the sexual wellbeing of BC patients, our systematic review reported the commonly used measurements to evaluate sexual wellbeing for women and men. There is a lack of consistent measures to assess sexual wellbeing in BC patients; in particular, there is a lack of validated questionnaires with appropriate psychometrics and social measures.

In our scoping review on physical activity interventions for BC patients, we reported on the structure and processes of physical activity interventions that may lead to better oncolgical outcomes. BC survivors were found to be more interested in an exercise program specially designed for them in a face-to-face format. Moreover, it was suggested that multimodal pre-habilitation consisting of patient information, physical activity, nutritional, and psychological optimization resulted in faster functional recovery.

Phase 2

By gathering insights from BC patients, their carers, and healthcare professionals in discussion groups (separate groups for mental, sexual, and physical wellbeing), phase 2 provided a better understanding of the problems and interventions needed to improve the BC patient experience. There was a clear overlap in needs with respect to mental, sexual, and physical wellbeing. More specifically, we identified a need for more information regarding the effects of BC treatments on HRQoL, as well as better patient-clinician relationship and psychological support. The discussion groups also clarified the types of services and support that would be preferred by BC patients.

Phase 3

By consulting our patient population, healthcare professionals, and the patient support groups on the findings of phase 1 and 2, we identified that many of the services and support needed by patients already existed within the hospital setting and the wider BC support groups; however, the lack of structured information summarizing these details was highlighted as the main barrier. There was a consensus that BC patients need more structured information regarding the impact of the disease, and treatment options, on mental and sexual wellbeing (Figure 2). In addition, it was noted that patients should be made aware of how physical activity may help their rehabilitation—and where to find correct guidance on how to engage in exercise.

To encourage a strong patient-healthcare professional relationship, there was also a consensus regarding the fact that nurses and clinicians would be best placed to deliver this information. However, it was noted that this information should be provided in a pragmatic way to avoid an increase in the workload of an already busy clinical service.

Hence, this consultation led to the development of a wellbeing program intervention in-line with the National Health Services (NHS) personalized care strategy.

Following the design of the intervention and resources, the expert group reached consensus on the feasibility study design. This trial aims to establish the feasibility of a wellbeing intervention for BC patients by providing a wellbeing information resource which is personalized and empowers these patients to improve several aspects of their own wellbeing (eg, mental, sexual, and physical). Providing patients with a clear and structured wellbeing resource, which is easily accessible and directs them to the relevant support, is thought to improve the patient experience. In turn, patients will be more likely to receive the care they need, which ultimately can prevent progression of their specific physical or psychosocial issues. The intervention entails the provision of a booklet and access to a website providing structured and detailed information on the services available to support patients with their mental and sexual wellbeing.
Figure 1. Flow diagram of modified MRC framework\(^\text{10}\) for developing complex interventions in the context of improving the BC patient wellbeing by addressing mental, sexual, and physical wellbeing. The current study specifically reports on phase 2, which aims to develop a theoretical understanding of the issues and interventions needs reported by patients.
as well as their physical activity engagement. The information given in the booklet and website has been developed with patients, healthcare professionals and patient support groups and will be designed by eCancer, an oncology communication charity aiming to raise the standards of care for cancer patients worldwide through education. In this way, bladder cancer patients have relevant resources in a single accessible location and may feel more empowered to seek further support resulting in a better patient experience and consequently HRQoL.

In our own hospital we intend to open this feasibility trial within the Graham Roberts Study—a Trials within Cohort (TWiCs) study for BC patients (REC Reference: 17/LO/1975; PI: Dr Van Hemelrijck). The description of this trial provides general details of the design as to facilitate implementation in other units. The study hypothesis is that a wellbeing intervention will increase patient awareness and adherence to the available services and will better support their needs and improve HRQoL. Therefore, this study will also help design a definitive RCT to test how the intervention affects HRQoL.

Appendix presents the further details of the protocol of this feasibility trial.

**Discussion**

Treatments for BC are associated with significant consequences, impacting on; patient body image, mental health, and social interactions. Nevertheless, there are remarkably few wellbeing interventions to specifically support BC patients and improve their experience throughout the care pathway. Here, we report on the development of a pragmatic wellbeing intervention which can be easily implemented into standard care.

The current standard of care in the UK establishes that a holistic assessment of cancer patients’ needs should be made to identify individualized packages of information and support at key points in their care (such as diagnosis, start or change of treatment, etc.). Although the need for a holistic approach to support BC patients has been recognized, phase 2 of our study showed that this has not been translated into better patient wellbeing support. We identified a need for more structured information regarding the effects of BC treatments on HRQoL, as well as better patient-clinician relationships and psychological support. Interestingly, a recent study by Rammant et al. based on 16 interviews with BC patients who underwent cystectomy also concluded that healthcare professionals play a critical role in providing information and psychological support during the BC patient pathway, including the postoperative phase where specific problems require additional information and practical guidance. Qualitative analyses of our phase 2 focus groups also noted that information on the type of services and support is needed to improve the BC patient experience. Due to the current lack of wellbeing interventions specifically designed for BC patients, this phase was crucial in understanding the optimal structure, content, and delivery method of our intervention.

Phases 1 and 2 of our work clearly showed that, in addition to the established need for a holistic approach, there is a need for a structured pathway to provide the relevant information. BC patients need to be more empowered and be aware of the services available to seek the help that they need throughout their care pathway. Patient empowerment is “a process in which patients understand their role, are given the knowledge and skills by their healthcare provider to perform a task in an environment that recognizes community and cultural differences and encourages patient participation.” Patients’ acquisition of sufficient knowledge to be able to engage with their healthcare provider as well as the presence of a facilitating environment have been defined as fundamental to this process of patient empowerment. Hence, the development of our pragmatic intervention providing structured information co-designed through engagement with patients, their carers, and healthcare professionals can help to facilitate the improvement of the BC patient experience through empowerment and engagement. Whilst this has not been specifically addressed for BC previously, Chua et al. assessed what information cancer patients want and also concluded that almost all patients want more information about the disease, tests and investigations, treatment, side-effects, sexuality, psychosocial support, and financial matters.

It is a strength of this study that throughout our approach we included a variety of resources and stakeholders. The literature reviews provided an overview of the published interventions and existing challenges that could be further...
explored in our qualitative analysis; this phase included several patients and patient involvement representatives who were the main source of insight to develop the wellbeing intervention. The COVID-19 pandemic environment limited the possibility to conduct this study to confirm its feasibility but by making this work available, we provide an opportunity to other hospitals to use this information and implement similar interventions to support their patients.

Conclusion

Our 3-phased development of an intervention to improve the BC patient experience identified the need for a pragmatic and holistic approach to patient wellbeing through patient and staff co-design. A feasibility trial has been proposed and other institutions are invited to use our wellbeing intervention to further evaluate its feasibility and acceptability and understand barriers to participation.

Appendix: Feasibility trial—Protocol

**Trial Objectives and Purpose**

The aim of this study is to assess the feasibility of a pragmatic wellbeing intervention compared to standard of care. The primary feasibility endpoint will be the patient adherence to the services offered. Secondary objectives include determining whether enrolling in the wellbeing intervention will improve HRQoL.

The study hypothesis is that a wellbeing intervention will increase patient awareness and adherence to the available services and will better support their needs and improving HRQoL.

**Study Design**

**Setting.** At Guy’s Cancer Centre, we have started recruitment to the Graham Roberts Study—a Trials within cohort (TWiCs) study for BC patients (REC Reference: 17/LO/1975; PI: Dr Van Hemelrijck). Since GSTT is a referral center, the Roberts Study also includes patients from secondary and tertiary hospitals. All patients will be eligible for the study following their first visit for a new or recurrent bladder cancer diagnosis. Patients with limited understanding of the English language and patients under the age of 18 years are ineligible. Each year, approximately 100 eligible patients visit GSTT for BC management.

The TWiCs design can be described as a large observational cohort of patients with a condition of interest for whom outcomes are regularly measured. Information from the cohort is then used to identify eligible patients for new RCTs. These patients are then randomized and only those assigned to the intervention arm will be contacted for further consent.

The outcomes of patients assigned to the intervention arm are then compared with outcomes of those eligible for the trial but assigned to receiving usual care. As outlined above, the Graham Roberts Study recruits patients at GSTT, London, UK.

**Participants.** Both newly diagnosed patients and patients with recurrent disease are eligible for the feasibility trial following their first visit after study start at GSTT for bladder cancer.

**Subject selection.** This trial will aim to recruit 40 bladder cancer patients from the Graham Roberts Cohort study. Twenty patients will be randomized to the intervention group and 20 patients for the control arm using an electronic data capture software.

The inclusion and exclusion criteria are described according to the Graham Roberts Cohort study.

**Inclusion criteria.** Bladder cancer patients who have provided written informed consent to be contacted for enrollment in an RCT embedded in the Graham Roberts study.

**Exclusion criteria.** Patients with limited understanding of the English language and patients under the age of 18 years are ineligible.

**Study design.** Eligible patients who provide written informed consent to enter the Graham Robert Study and to enroll into further studies will be randomized to enter the study arm or the control arm in 1:1 ratio. Patients randomized to the intervention arm will be contacted by a clinical nurse specialist or research nurse/coordinator. The patient information sheet will be sent to patients and those who are willing to enroll into the wellbeing feasibility intervention will be required to sign the consent form.

In their next appointment, one of the study coordinators (e.g., clinical nurse specialist, research nurse, and trial coordinator) will provide patients with the wellbeing booklet and access to the website as well as any further clarification needed.

The booklet will serve as a short summary and highlight the support and services available to patients as well as the calendar for the seminars. The seminars will be incorporated into the monthly BC support groups already available every 2 months. A different speaker for each topic will be invited. All seminars are optional, and patients are not obliged to attend.

The website will provide access to more comprehensive information regarding patients’ wellbeing as well as direct links to other services and supports provided within or outside GSTT NHS Foundation Trust, such as ACBUK and Fight Bladder Cancer. Patients in the study arm will be provided with the URL to the website as well as with their unique login/password details.
**Data Collection**

All eligible patients who provide written informed consent are asked to fill out the baseline questionnaire of the Roberts Study—which includes the QoL FACT-BI questionnaire. Moreover, information is collected about demographics, medical history, history of tobacco consumption, information about current alcohol, smoking, and environmental exposures, fatigue (FACIT), anxiety and depression (PHQ-9), health questionnaire (EQ-5D-5L), physical activity, and dietary habits.

Additionally, information consulted through the website provided as well as attendance to the seminars will also be collected as part of their standard care.

The Graham Roberts Study serves as the infrastructure to start a wellbeing feasibility study and allows us to compare the wellbeing intervention with standard of care for bladder cancer.

Neither patients nor treating healthcare professionals will be blinded for allocated group assignment since both will need to know what information to provide to which patient.

After every patient has completed a 12 months period in the trial, overall insight from the feasibility trial will be collected through an evaluation form. We will also conduct a qualitative analysis through interviews; this will help to understand the effect of the possible contamination of the control group and also understand the experience of patients in the intervention arm in more detail.

**Study Endpoints**

**Primary endpoint.** The intervention arm will participate in the above-defined wellbeing intervention, while the control arm will receive standard care. Endpoints for both arms are being collected over 12 months as per the Graham Roberts study protocol.

The primary endpoint of this study is to assess feasibility. More specifically, the following feasibility outcomes will be collected:

1. Recruitment and eligibility: number of people identified in the Roberts study, percentage of people interested in participation, assessed for eligibility, meeting inclusion criteria and included reasons for ineligibility, reasons for non-participation
2. Evaluation of feasibility and acceptability through qualitative analyses using semi-structured interviews for patients who consented to the intervention arm and those who declined to participate in the trial (if they agree to participate in the interviews). This will allow us to evaluate for reasons for (poor) attendance and withdrawal as well as explore the impressions and experiences of working with the intervention (both from the participant and healthcare professionals point of view).

**Secondary endpoint.** The secondary endpoints are:

1. HRQoL.
2. Fatigue.
3. Depression.
4. Physical activity.
5. Assessment of dietary habits.
6. Sexual wellbeing.

Data on secondary endpoints will be collated every 6 months as per the Graham Roberts Cohort Study protocol (please note that an amendment is pending to make this 6 months). A clinical nurse specialist or research nurse/coordinator will contact patients to collect the data. The first report will be prepared within 12 months after the enrollment phase is completed.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was funded by Arcobaleno Cancer Trust and Action Bladder Cancer UK.

**ORCID iD**

Agustina Bessa https://orcid.org/0000-0001-7196-2280

**References**

1. NICE. Bladder cancer: diagnosis and management management. NICE guideline. 2015. Accessed August 2, 2019. https://www.nice.org.uk/guidance/ng2
2. Bryan RT, Kirby R, O’Brien T, Mostafid H. So much cost, such little progress. *Eur Urol*. 2014;66(2):263-264.
3. Svanek RS, Hollenbeck BK, Holmäng S, et al. The economics of bladder cancer: costs and considerations of caring for this disease. *Eur Urol*. 2014;66(2):253-262.
4. WHO. *WHOQOL: Measuring Quality of Life*. WHO; 2014. Accessed October 1, 2019. https://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/
5. Healthy People. Health-related quality of life and well-being. *Healthy People 2020*. Accessed October 1, 2019. https://www.healthypeople.gov/2020/about/foundation-health-measures/Health-Related-Quality-of-Life-and-Well-Being
6. World Health Organization. Promotion of mental well-being. *SEARO*. 2017. Accessed September 22, 2019. http://www.searo.who.int/entity/mental_health/promotion-of-mental-well-being/en/
7. Pham H, Torres H, Sharma P. Mental health implications in bladder cancer patients: a review. *Urol Oncol Semin Orig Investig*. 2019;37(2):97-107.
8. Dunn MW. Bladder cancer: a focus on sexuality. *Clin J Oncol Nurs*. 2015;19(1):68-73.
9. Chappidi MR, Kates M, Sopko NA, et al. Erectile dysfunction treatment following radical cystoprostatectomy: analysis of a
nationwide insurance claims database. *J Sex Med*. 2017;14(6):810-817.

10. Craig P. Developing and evaluating complex interventions. 2019. Accessed February 15, 2019. https://www.mrc.ac.uk/complexinterventionsguidance

11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.

12. Bessa A, Martin R, Häggström C, et al. Unmet needs in sexual health in bladder cancer patients: a systematic review of the evidence. *BMC Urol*. 2020;20(1):64.

13. Bessa A, Rammant E, Enting D, et al. Urological cancers and mental wellbeing: are we helping our patients? A systematic review of supportive interventions. *PLoS One*. 2020.

14. Bessa A, Bosco C, Mehrotra S, et al. Is there a role for physical activity interventions in the treatment pathway of bladder cancer?: a scoping review of the literature. *BMJ Open Sport Exerc Med*. 2021;7(1):e000951.

15. Mehrotra S, Rowland M, Zhang H, et al. Scoping review protocol: is there a role for physical activity interventions in the treatment pathway of bladder cancer? *BMJ Open*. 2019;9(11):e033518.

16. Bessa A, Bosco C, Cahill F, et al. How can we improve the bladder cancer patient experience? Insights from a focus group round focused on mental, sexual, and physical wellbeing. EAUN conference 2020.

17. NHS England. Personalised care. Accessed April 29, 2021. https://www.england.nhs.uk/personalisedcare/

18. ecancer. Accessed November 7, 2020. https://ecancer.org/en/

19. BCAN. Survivorship and quality of life – bladder cancer advocacy network. 2020. Accessed November 7, 2020. https://bcan.org/bladder-cancer-survivor/

20. NICE. Treating non-muscle-invasive bladder cancer | information for the public | bladder cancer: diagnosis and management | guidance | NICE. 2015. Accessed September 20, 2019. https://www.nice.org.uk/guidance/ng2/ifp/chapter/treating-non-muscle-invasive-bladder-cancer

21. Rammant E, Fonteyne V, Van Goethem V, et al. Supportive roles of the healthcare team throughout the illness trajectory of bladder cancer patients undergoing radical cystectomy: a qualitative study exploring the patients’ perspectives. Under revision

22. WHO. The *WHO Health Promotion Glossary*. WHO; 2010. Accessed November 2, 2020. https://www.who.int/healthpromotion/about/HPG/en/

23. Chua GP, Tan HK, Gandhi M. What information do cancer patients want and how well are their needs being met? 2018;12:873.

24. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract*. 2004;10(2):307-312.

25. Browne RH. On the use of a pilot sample for sample size determination. *Stat Med*. 1995;14(17):1933-1940.

26. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *J Clin Epidemiol*. 2011;65:301-308.

27. Wylie H, Cahill F, Santaolalla A, et al. Graham Roberts study protocol: first “trials within cohort study” for bladder cancer. *BMJ Open*. 2019;9(9):e029468.