PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Graham Roberts Study Protocol: a first "Trials within Cohort study" for bladder cancer
AUTHORS	Wylie, Harriet; Cahill, Fidelma; Santaolalla, Aida; Moss, Charlotte; Enting, Deborah; Amery, Suzanne; Chatterton, Kathryn; Khan, Muhammad; Bryan, Richard; Gillett, Cheryl; Josephs, Debra; Chowdhury, Simon; Rudman, Sarah; Hughes, Simon; Relton, Clare; Van Hemelrijck, Mieke

VERSION 1 - REVIEW

REVIEWER	Alina Vrieling, Assistant Professor Radboud university medical center, The Netherlands
REVIEW RETURNED	05-Mar-2019

GENERAL COMMENTS	General points: This is an interesting study protocol of a bladder cancer cohort with a trials within cohort (TwiCs) design. However, there are several points for improvement. The current text is very long and is partly repeating itself, and should be written much more concise. Not all methods have been clearly described, and there are some inconsistencies throughout the text. The text is currently not in the right format for BMJ Open (e.g. abstract, headings, references), and a paragraph on Dissemination is missing. Specific points: - Abstract: The abstract should be structured in Introduction, Methods and analysis, and Ethics and dissemination (needs to be added). Discussion should be left out. - Background: The background can be more concise and is not logically structured. Line 81 – 84 can be left out. Line 87 – 96 are not very informative for the current study and can be described more concise. It would be more informative to read what are the current problems with RCTs in bladder cancer which can be reduced using the current design (other than that there is less research into bladder cancer compared to other cancers) and why the TwiCs design would provide the most efficient and high impact research strategy for bladder cancer patients in the UK, maybe using line 106 – 123 from the Methods. There, the information is not in place because it is more general than specific for the current study. Line 74 – 79 about the current study can be mentioned at the end of the background, before the objectives. - Line 126 – 131: Different hospital/centre names are used. Guy's hospital is the same as GSTT? And it concerns the Urology Centre of the GSTT? Please be consistent for clarity. How many secondary

	and tertiary hospitals are referring to GSTT? - Line 133 – 139: Has the appointment with the direct clinical care team already been made beforehand. This seems otherwise quite infeasible, or are patients already present one hour before their first appointment with the Consultant? Explanation + filling out questionnaires has to be done within 30 minutes? Consider rephrasing to make this more clear. - Line 143 – 145: Is a written informed consent obtained after the follow-up call? - Line 147 – 164: The staged informed consent procedure has not been clearly described. Does the first written informed consent after the research consultation or follow-up call only include the consent for the questionnaires, or also for collection and use of clinical data (or is this later and when?)? When exactly are patients invited to consent for the biobank? After they have completed the baseline questionnaire or at another time point? And for the random allocation to experimental intervention? Or are they asked for consent for the parts belonging to the cohort at one time point and for allocation to experimental intervention at another time point, or all at the same time point? Please describe this more clearly and consider numbering/bulleting the different types of consent. - Line 172 – 176: What is meant with 'asymmetric treatment'? - Line 178 – 186: Consider mention patient and public engagement later in the Methods section. - Line 189: What is an active new bladder cancer diagnosis? This does not seem common terminology. Consider using 'incident bladder cancer diagnosis'. - Line 193 – 195: The exclusion criteria are redundant and can be left out. - Line 201, 289: Combine the paragraphs "Expected duration of the study" and "Sample size" in one paragraph. - Line 209 – 225: This has already been largely described in line 133 – 145, but the information provided slightly differs. A follow-up call (line 143 – 145) is not mentioned here. Line 229 – 231 and line 265 – 268: Information on questionnaires is repeated. Please try to be more concise and consistent, and leave out redundant information. I think the paragraph "Study procedures by visit" can be entirely deleted. - Line 233 – 241: Please report this information at the same place as the other information about informed consent is reported. - Line 259: Why are data collected for participants undergoing radical cystectomy presented in a separate table (partly repeating data collected for other participants) and data collected for the other patients in the text? Consider reporting all collected data in a table. Heading of table should be above and not below the table. What type of imaging data are collected? This is not further specified. - Line 262: Will information on progression also be collected? - Line 292 – 299: Why are the Umbrella study response rates mentioned in detail but not used for the calculation of the recruitment rate of this proposed study? The expected recruitment rate of 53% (400 / (5*150) for the current study is much lower than that reported by the Umbrella study (88%). What is this based on? In line 130, it is mentioned that 100 eligible instead of 150 eligible patients are seen per year, so this is inconsistent. - Is this number sufficient for randomisation to trials, since patients of different disease stages are included and patients with both incident and recurrent tumours are included? - Line 301 – 327: This part on direct access to source data and documents is very detailed and could be described more concise, and could be combined with line 350 – 357 on data handling. Line

	357 is not very informative as the data management plan is not provided. - Line 386 – 389: Consider writing the trial status in text and providing some more information. How many patients are currently included?

REVIEWER	Colin Dinney, MD University of Texas MD Anderson Cancer Center, Houston, TX, USA None relevant to the study reviewed. Other disclosures: FKD Therapies Oy - Consulting Merck – Consulting & Research Janssen – Consulting NCI – Consulting & Research The University of Eastern Finland, Faculty of Health Sciences (UEFHS) - Research
REVIEW RETURNED	21-Mar-2019

GENERAL COMMENTS	This is an interesting project proposal that in essence allows for a formalized, large scale collection of observational data prospectively from patients diagnosed with bladder cancer, while also allowing for the same patients to be selected from for a future, as of yet undefined, randomized controlled trial. In essence, patients will be randomly selected for an unspecified future intervention with the remaining patients available for analysis as a comparator arm of usual care. In addition, the use of standardized patient related outcome metrics will allow for improved understanding of the disease and existing therapy's impact on patient quality of life. The study proposal is well written and prior precedent exists in other disease states as the authors note. - The validated questionnaires that are planned to be administered cover domains related to quality of life, fatigue, depression, standardized health outcomes, physical activity, and assessment of dietary habits. - No interventions are currently planned as part of the protocol as written. - The authors report that without a primary research question, no sample size calculations have been performed; prior similar studies reportedly had 80% baseline questionnaire return rate and up to 74% return rate for follow-up. This seems higher than would be expected from a bladder cancer patient population that is typically older and potentially less familiar with tablets/computer-based surveying techniques, at least in our experience. - Trials within cohort studies such as the one proposed have been criticized for ethical concerns; for example, in the proposal, the authors note that informed consent is obtained "asymmetrically," in that patients give consent up front to be randomly allocated to unspecified experimental intervention in the future. However, only patients who end up being randomly selected to the intervention arm are offered the experimental intervention (the other patients are not notified). The authors note in the protocol that "patients who are randomly allocated to the control arm will…receive standard of care [but] are not informed about their participation in the control arm" (since they gave consent in the beginning). Can the authors comment on whether they plan to address the concerns regarding trial ethics directly with the patients at the time of eligibility (as the design can be confusing to the lay person—is this nuance detailed to them), and are there specific future trials/interventions planned

	that can be discussed in greater detail within this protocol? - The other concern with the protocol is the timing of consent – the authors indicate they plan to obtain informed consent and educate patients on the trial if they are fairly certain the patients will have a diagnosis of bladder cancer in the near future. Obviously, the time of diagnosis can be a time of some degree of stress for any patient or loved one worried about a new cancer diagnosis—what safeguards are in place to mitigate potential undue pressure a patient might feel to sign up for the trial if it's pitched so close to the time of their original diagnosis/just prior to their first biopsy?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

This is an interesting study protocol of a bladder cancer cohort with a trials within cohort (TwiCs) design. However, there are several points for improvement. The current text is very long and is partly repeating itself, and should be written much more concise. Not all methods have been clearly described, and there are some inconsistencies throughout the text. The text is currently not in the right format for BMJ Open (e.g. abstract, headings, references), and a paragraph on Dissemination is missing.

We would like to thank the reviewer for their detailed feedback and agree with all their comments relating to text length, paper style and structure as raised above. As such, the full text has now been consolidated and appears in a more concise manner. The methodology has been restructured and altered for ease of reading and understanding. The inconsistencies identified throughout the text have been corrected and the formatting of the submission has been changed to be in line with the specific requirements of BMJ Open.

Specific points:

- Abstract: The abstract should be structured in Introduction, Methods and analysis, and Ethics and dissemination (needs to be added). Discussion should be left out.

Response: Thank you for highlighting our error in the structuring of the abstract section. We have now altered this section to be in line with the requirements of the journal and included a short overview on Ethics and Dissemination.

- Background: The background can be more concise and is not logically structured. Line 81 – 84 can be left out. Line 87 – 96 are not very informative for the current study and can be described more concise. It would be more informative to read what are the current problems with RCTs in bladder cancer which can be reduced using the current design (other than that there is less research into bladder cancer compared to other cancers) and why the TwiCs design would provide the most efficient and high impact research strategy for bladder cancer patients in the UK, maybe using line 106 – 123 from the Methods. There, the information is not in place because it is more general than specific for the current study. Line 74 – 79 about the current study can be mentioned at the end of the background, before the objectives.

Response: We thank the reviewer for their feedback on the background section of this paper. We have worked to restructure this section of the protocol, removing specific sections of text as indicated and including concise information on the background of TwiCs and specific advantages of utilising this

study design for efficient and high impact research in bladder cancer. We hope that this section of the protocol is now more logical and informative to the reader.

- Line 126 – 131: Different hospital/centre names are used. Guy's hospital is the same as GSTT? And it concerns the Urology Centre of the GSTT? Please be consistent for clarity. How many secondary and tertiary hospitals are referring to GSTT?

Response: Thank you for highlighting the inconsistencies of the hospital centre/names used throughout the text. The Trust encompasses two NHS hospitals based in South London with each centre covering different specialities. All oncology patients are seen and treated at the Urology Centre of the Guy's hospital site but, for clarity, we have now altered this to appear simply as Guy's and St Thomas' NHS Foundation Trust (GSTT) throughout the text. It is, unfortunately, difficult to quantify the number of referring hospitals each year as patients can request to attend GSTT for their bladder cancer care from any NHS Foundation across the United Kingdom.

- Line 133 – 139: Has the appointment with the direct clinical care team already been made beforehand. This seems otherwise quite infeasible, or are patients already present one hour before their first appointment with the Consultant? Explanation + filling out questionnaires has to be done within 30 minutes? Consider rephrasing to make this more clear.

Response: We thank the reviewer for highlighting this point. This section of the methodology has been rephrased to make the process around patients being approached to take part in the study more understandable to the reader. The patient population approached for inclusion in the Graham Robert's Study will have already undergone diagnostic investigations and will be attending the clinic to receive their initial diagnosis or news of disease recurrence. The patient is approached by the research team with information about the Graham Robert's Study once diagnosed and can provide full informed consent on that date or at a later clinic appointment. Patients are provided with the questionnaire after consenting and are able to complete in clinic or take home for completion.

- Line 143 – 145: Is a written informed consent obtained after the follow-up call?

Response: Thank you for your comment on the process of informed consent after a follow-up phone call. A follow-up phone call is provided to patients who are not ready to discuss the study at their initial appointment. If, during the phone call, the patient expresses their wishes to take part in the Graham Robert's Study, they are approached at their next clinical appointment to provide full written informed consent.

- Line 147 – 164: The staged informed consent procedure has not been clearly described. Does the first written informed consent after the research consultation or follow-up call only include the consent for the questionnaires, or also for collection and use of clinical data (or is this later and when?)? When exactly are patients invited to consent for the biobank? After they have completed the baseline questionnaire or at another time point? And for the random allocation to experimental intervention? Or are they asked for consent for the parts belonging to the cohort at one time point and for allocation to experimental intervention at another time point, or all at the same time point? Please describe this more clearly and consider numbering/bulleting the different types of consent.

Response: We would like to thank the reviewer for raising the point that the staged informed consent procedure is difficult to follow. We have now included bullet points within the Methods/Design section of the text to fully explain and illustrate the consenting process for the study.

- Line 172 – 176: What is meant with ‘asymmetric treatment’?

Response: In the context of the TwiCs design, ‘asymmetric treatment’ is defined as a process whereby those patients selected for the experimental arm provide informed consent for the intervention trial, while data for the control arm is based on prior broad permission. This definition has been made clearer within the text of the protocol.

- Line 178 – 186: Consider mention patient and public engagement later in the Methods section.

Response: We thank the reviewer for their suggestion to move the patient and public engagement section of the text to later in the Methods section. We have taken this feedback onboard and moved patient and public engagement to after the ‘Assessment of safety’ section.

- Line 189: What is an active new bladder cancer diagnosis? This does not seem common terminology. Consider using ‘incident bladder cancer diagnosis’.

Response: Thank you for raising this issue with non-common terminology included within the text. This has been altered within the inclusion criteria to appear as ‘appointment for a new or recurrent diagnosis of bladder cancer’.

- Line 193 – 195: The exclusion criteria are redundant and can be left out.

Response: The exclusion criteria have been removed from the text.

- Line 201, 289: Combine the paragraphs “Expected duration of the study” and “Sample size” in one paragraph.

Response: Thank you for your comment on combining the paragraphs ‘Expected duration of the study’ and ‘sample size’. This suggestion has been taken onboard and implemented within the text.

- Line 209 – 225: This has already been largely described in line 133 – 145, but the information provided slightly differs. A follow-up call (line 143 – 145) is not mentioned here. Line 229 – 231 and line 265 – 268: Information on questionnaires is repeated. Please try to be more concise and consistent, and leave out redundant information. I think the paragraph “Study procedures by visit” can be entirely deleted.

Response: We thank the reviewer for identifying the inconsistencies within the “Study procedures by visit” section of the text. In line with ensuring the text is as concise and consistent as possible, we have deleted this section of text from the submission.

- Line 233 – 241: Please report this information at the same place as the other information about informed consent is reported.

Response: Thank you for requesting that this information appears in the same place as the section on informed consent. The protocol has been altered to fit with this request.

- Line 259: Why are data collected for participants undergoing radical cystectomy presented in a separate table (partly repeating data collected for other participants) and data collected for the other patients in the text? Consider reporting all collected data in a table. Heading of table should be above and not below the table. What type of imaging data are collected? This is not further specified.

Response: We thank the reviewer for her comments relating to the data items collected as part of the Graham Robert's Study. The text has now been amended to specify the type of imaging data which is collected (CT and MRI). The heading of the table has been moved to above the table- thank you for noticing this. The radical cystectomy data has been reported in a separate table due to the large number of data items available and the fact that this information will not be available for all patients enrolled in the Graham Robert's Study. The core clinical data items which will be routinely collected appear within the text body.

- Line 262: Will information on progression also be collected?

Response: As part of the Graham Robert's study, information on disease progression will be collected. The protocol has been amended to state this.

- Line 292 – 299: Why are the Umbrella study response rates mentioned in detail but not used for the calculation of the recruitment rate of this proposed study? The expected recruitment rate of 53% (400 / (5*150) for the current study is much lower than that reported by the Umbrella study (88%). What is this based on? In line 130, it is mentioned that 100 eligible instead of 150 eligible patients are seen per year, so this is inconsistent.

- Is this number sufficient for randomisation to trials, since patients of different disease stages are included and patients with both incident and recurrent tumours are included?

Response: We thank the reviewer for querying the inconsistencies associated with utilising the Umbrella study response rates in this protocol. So as to avoid further confusion and inconsistency, the authors have decided to remove this section from the text and replace it with an update into the recruitment of the study specifically. The authors believe that this will provide more useful insight to the reader. We thank the reviewer for also enquiring whether the numbers of bladder cancer patients recruited will be sufficient for randomisation for trials. Although no trials are currently planned, it is expected that initial interventions will be pilot studies which require a much smaller number of participants.

- Line 301 – 327: This part on direct access to source data and documents is very detailed and could be described more concise, and could be combined with line 350 – 357 on data handling. Line 357 is not very informative as the data management plan is not provided.

Response: The section on source data and documents has now been combined and amended to be more concise. We thank the reviewer for their comments on the necessity of such detailed information when a data management plan is not provided with the protocol.

- Line 386 – 389: Consider writing the trial status in text and providing some more information. How many patients are currently included?

Response: We thank the reviewer for her query relating to the numbers of patients currently included within the study. The sample size section of the protocol text has now been updated with the most up-to-date recruitment numbers and now reads:

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

Reviewer 2

This is an interesting project proposal that in essence allows for a formalized, large scale collection of observational data prospectively from patients diagnosed with bladder cancer, while also allowing for the same patients to be selected from for a future, as of yet undefined, randomized controlled trial. In essence, patients will be randomly selected for an unspecified future intervention with the remaining patients available for analysis as a comparator arm of usual care. In addition, the use of standardized patient related outcome metrics will allow for improved understanding of the disease and existing therapy’s impact on patient quality of life. The study proposal is well written and prior precedent exists in other disease states as the authors note.

- The validated questionnaires that are planned to be administered cover domains related to quality of life, fatigue, depression, standardized health outcomes, physical activity, and assessment of dietary habits.

- No interventions are currently planned as part of the protocol as written.

- The authors report that without a primary research question, no sample size calculations have been performed; prior similar studies reportedly had 80% baseline questionnaire return rate and up to 74% return rate for follow-up. This seems higher than would be expected from a bladder cancer patient population that is typically older and potentially less familiar with tablets/computer-based surveying techniques, at least in our experience.

Response: We thank the reviewer for his comment on the predicted uptake rate of the bladder cancer patient population into the Graham Robert’s study. We agree that some of the older patients may potentially be less familiar with tablet/computer-based surveying and hence will make every effort to provide consenting patients with paper-based questionnaires for completion if deemed more appropriate. Additionally, the ‘Expected duration of the study and sample size’ section of the protocol

has now been updated to include up to date numbers on consented patients and baseline questionnaires completed. This should give the reader further insight into the timelines of the study and projected date of completion of baseline recruitment. The text has been updated to:

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

- Trials within cohort studies such as the one proposed have been criticized for ethical concerns; for example, in the proposal, the authors note that informed consent is obtained “asymmetrically,” in that patients give consent up front to be randomly allocated to unspecified experimental intervention in the future. However, only patients who end up being randomly selected to the intervention arm are offered the experimental intervention (the other patients are not notified). The authors note in the protocol that “patients who are randomly allocated to the control arm will…receive standard of care [but] are not informed about their participation in the control arm” (since they gave consent in the beginning). Can the authors comment on whether they plan to address the concerns regarding trial ethics directly with the patients at the time of eligibility (as the design can be confusing to the lay person—is this nuance detailed to them), and are there specific future trials/interventions planned that can be discussed in greater detail within this protocol?

Response: Thank you for raising the potential ethical concerns associated with the trials within cohort study design. We agree that this study design has the potential to cause confusion to the bladder cancer patient population and hence the clinical and research teams make every effort to explain the study design in detail to the patient prior to obtaining informed written consent. The research team are also provided with visual aids which explain the TwiCs design in layman terms and are able to use these as an aid when explaining the study design to the patient. The bladder cancer patients are unable to provide full informed written consent until the research team are sure they fully understand the study process.

We thank the reviewer for enquiring as to whether there are any specific future trials/interventions planned which could be included in greater detail within the protocol. Unfortunately, at present, there are no such planned interventions. The research team hope, that as consented patient numbers increase, an intervention or trial will be implemented. This will probably not occur until year 2 or 3 of recruitment, however.

- The other concern with the protocol is the timing of consent – the authors indicate they plan to obtain informed consent and educate patients on the trial if they are fairly certain the patients will have a diagnosis of bladder cancer in the near future. Obviously, the time of diagnosis can be a time of some degree of stress for any patient or loved one worried about a new cancer diagnosis—what safeguards are in place to mitigate potential undue pressure a patient might feel to sign up for the trial if it’s pitched so close to the time of their original diagnosis/just prior to their first biopsy?

Response: Thank you for raising this concern relating to the timing of consent of bladder cancer patients, after a new cancer diagnosis. The authors agree that a new cancer diagnosis is associated with a degree of stress and upset for any patient or loved one and hence the clinical and research teams undergo special training to deal with such sensitive situations. If a patient shows signs of upset or distress at initial appointment, the clinical team will not approach him/her regarding the study until a subsequent clinical appointment.

VERSION 2 – REVIEW

REVIEWER	Alina Vrieling, Assistant Professor Radboud University Medical Center, The Netherlands
REVIEW RETURNED	09-May-2019

GENERAL COMMENTS	This manuscript has substantially improved after revision. It is now in the right format, much more concise, and much better readable. There are some minor revisions needed, as listed below. Line 38: Replace 'active new' by 'new' Line 60: Change 'generates a of wide' to 'generates a wide' Line 129/182: Replace 'Robert's' by 'Roberts' Line 181: Please also mention the starting date of the study, so it is clear in which time frame the 72 patients have been recruited. How many patients have been approached from this starting date up to April 2019 and what was the response rate? Line 232/233: When 100 eligible patients are seen per year, and at least 400 are expected to be recruited over a period of 5 years, you seem to expect a response rate of 80%. Is this in line with what you have seen so far? See also previous comment. Line 272: Replace 'study will be to' by 'study will be performed to' Line 321: Here it is stated that recruitment started 22nd February 2018. Since 72 patients have been recruited up to April 2019 over a period of more than one year (with 64 completing questionnaires, so ~10% drop-out), the 80% response rate and recruitment of 400 patients in 5 years seems too optimistic. Please clarify this. Line 322: Projected data of recruitment completion is 28th October 2022 while in line 184 31st December 2022 is mentioned. Which one is correct? Page 8, Table 1: Lay-out not correct in PDF file but correct in Word file.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

Line 38: Replace 'active new' by 'new'

Response: We have amended this sentence to omit the use of the word 'active'. The sentence now reads; "Using the TwiCs design, we will recruit patients aged 18 or older who are willing and able to provide signed informed consent and have a diagnosis of new or recurrent bladder cancer into this prospective cohort study.".

Line 60: Change 'generates a of wide' to 'generates a wide'

Response: Thank you for noticing this typographic error. We have amended this sentence to now read correctly.

Line 129/182: Replace ‘Robert’s’ by ‘Roberts’

Response: We would like to thank the reviewer for noticing this grammatical error throughout the manuscript. We have now amended all such errors so the study name remains consistent.

Line 181: Please also mention the starting date of the study, so it is clear in which time frame the 72 patients have been recruited. How many patients have been approached from this starting date up to April 2019 and what was the response rate?

Response: We would like to thank the reviewer for her comments regarding clarity on the study timeframes to date. The date of recruitment of the first patient has been added into the main body of text and the date of commencement of recruitment adjusted accordingly. The authors have also included details on the number of patients approached with a patient information sheet compared to those who have provided full written informed consent to highlight current response rates. Additionally, more up to date data on the number of patients who have completed their baseline questionnaire has been added into this revision:

“Recruitment to the Graham Roberts Study commenced on 23rd March 2018. At the point of submission of this protocol (April 2019), 84 bladder cancer patients had been approached with a patient information sheet, and 72 patients had provided full written informed consent and completed the baseline study questionnaire.”

Line 232/233: When 100 eligible patients are seen per year, and at least 400 are expected to be recruited over a period of 5 years, you seem to expect a response rate of 80%. Is this in line with what you have seen so far? See also previous comment.

Response: thank you for raising this point on expected vs current response rates. The authors have included further information about these rates as well as a projected date of recruitment completion should response rates remain consistent throughout the study. The authors hope, however, that as the study continues, the direct clinical care team and research staff will become more proficient at identifying eligible patients and approaching them regarding the study- thus increasing response rates. The study is also limited by dates agreed as part of ethical clearance but minor amendments shall be made in the future should the authors need to extend the recruitment period.

“At current rates of consent, the authors project the baseline recruitment of 400 bladder cancer patients to be complete by 31st August 2023. It is expected, however, that recruitment rates will increase as the direct clinical care team and research nurses/assistants become more efficient at identifying and approaching eligible patients. The projected end of recruitment date is therefore set at 31st December 2022. Moreover, ethical clearance is in place to recruit until this date.”

Line 272: Replace ‘study will be to’ by ‘study will be performed to’

Response: we would like to thank the reviewer for noticing this omission of the word performed. This sentence has now been altered to read correctly.

Line 321: Here it is stated that recruitment started 22nd February 2018. Since 72 patients have been recruited up to April 2019 over a period of more than one year (with 64 completing questionnaires, so

~10% drop-out), the 80% response rate and recruitment of 400 patients in 5 years seems too optimistic. Please clarify this.

Response: thank you for raising this point about response rates. As above, we have now included a projected date of recruitment completion based on current consent rates. If necessary, a minor amendment will be submitted to the ethics board to gain additional time to recruit the 400 bladder cancer patients into the study.

Line 322: Projected data of recruitment completion is 28th October 2022 while in line 184 31st December 2022 is mentioned. Which one is correct?

Response: thank you for identifying the difference in dates of recruitment completion throughout the text. We have now made this consistent throughout the document as the 31st December 2022, in line with current ethical clearance.