PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>TripleAIM1: a nationwide registry of de novo metastatic hormone sensitive prostate cancer with prospective quality-of-life assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>van Elst, Tessa; van Basten, Jean-Paul; van den Berg, Pieter; van den Bergh, Roderick; Bloem, Sjaak; van Dodewaard-de Jong, Joyce; Hendriks, Mathijs; Klaver, Sjoerd; Lalmahomed, Zari; Luijendijk, Daphne; van de Luijtgaarden, Addy; Roelofs, Luc; Vis, André; Vreugdenhil, Gerard; Vrijhof, Eric; Wijsman, Bart; Bloemendal, Haiko; Mulders, Peter; Mehra, Niven</td>
</tr>
</tbody>
</table>

VERSION 1 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Victor Kyaruzi Muhimbili University of Health and Allied Sciences, General Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVIEW RETURNED</td>
<td>20-Apr-2023</td>
</tr>
</tbody>
</table>

GENERAL COMMENTS

<table>
<thead>
<tr>
<th>PATIENT POPULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>The author mentioned that for patient to be recruited must have a complete radiological work up for metastasis confirmation, can you describe the radiological gestures available in the mentioned 14 hospitals i.e Lumbosacral Xray?, CT scan?, Bone Scan? MRI? PET-Scan? however did not mention the role of radiological work up for follow up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SAMPLING</th>
</tr>
</thead>
<tbody>
<tr>
<td>- The author described the selection procedure but the sampling technique was not stated i.e simple random sampling or convenient sampling</td>
</tr>
<tr>
<td>- The sample size calculation is not clear, the author stated that the sample size was specified because of retrospective study design involvement, this reason does not suffice the justification, in my view the sample size specification for this design could not be deducted because the study intends to evaluate the overall data for de novo metastatic hormonal sensitive prostate cancer in Netherland for a specified time.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TREATMENT STRATEGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>The author did not clarify how the randomization and blinding will be approached to optimize 75 for each interventional arm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DATA COLLECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>The author mentioned the source of data such as LOGEX, CTcue and IKNL tools, could you clarify how the reliability and validity of these tools were tested?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QUESTIONNAIRES</th>
</tr>
</thead>
<tbody>
<tr>
<td>- The author described to evaluate the PROM using EORTC-C 30,</td>
</tr>
</tbody>
</table>
EPIC-26, FACT-Taxane, BPI-SF, FACIT-Fatigue and FACT-Cognitive. The author did enumerate Taxane in the treatment strategy then why should the FACT-Taxane be employed?
- In the eligibility criteria the authors mentioned to exclude all cognitive impaired patients on the other hand you intend to use the FACT-Cognitive to evaluate HRQoL this portends the data to high risk of bias (ROB) because majority of patients with the interest of outcome for QoL will be excluded.
- The author also mentioned to exclude patients who are not fluent Dutch speakers, however all the Questionnaires enumerated for assessment of QoL exist in English language can you clarify whether the validated Dutch language versions exist and if not how do you plan to translate and test them for reliability and validity?

ENDPOINTS
The author mentioned the primary endpoints as the QoL derived from the EORTC-QLQ-C30 score, however the time to event endpoints such as PFS and OS were not mentioned.
- On the data collection the author described how the cost variable as the outcome of interest collected by DBC, however it is not mentioned on this section

DATA ANALYSIS
The author did not explain how the cost effectiveness data is planned to be analyzed i.e Cost effectiveness Increment Ratio and Quadrant

REVIEWER
F Drummond
University College Cork National University of Ireland, Department of Epidemiology and Public Health

REVIEW RETURNED
25-Apr-2023

GENERAL COMMENTS
The authors describe the establishment of a nationwide registry of de novo metastatic hormone sensitive prostate cancer with prospective quality-of-life assessment. They important study will analyse a retrospective cohort and will collate a prospective cohort, amassing a large amount of data on QoL, survival and financial data which will measure the impact of different treatment modalities, and which may ultimately impact the future, personalised treatment of this patient cohort.

VERSION 1 – AUTHOR RESPONSE
Reviewer 1:
We express our gratitude to Reviewer 1 for conducting an extensive review of our manuscript and providing numerous valuable suggestions for improvement. We have diligently addressed all the raised concerns in this rebuttal.

PATIENT POPULATION
Comment 1: The author mentioned that for patient to be recruited must have a complete radiological work up for metastasis confirmation, can you describe the radiological gestures available in the mentioned 14 hospitals i.e Lumbosacral Xray?, CT scan?, Bone Scan? MRI? PET-Scan? however did not mention the role of radiological work up for follow up

Response to comment 1: The reviewer suggested to provide more detailed information about the diagnostic modalities available in the 14 hospitals for detecting metastases. We have added the available modalities we deemed acceptable for staging metastatic hormone sensitive prostate cancer (line 101-103). Secondly, the reviewer suggests to mention the role of radiological work up for follow-
up. As this study is observational we did not interfere with daily practice and collect data of all radiological modalities to ascertain progressive disease.

Comment 2: The author also mentioned the baseline PSA of > 100ng/ml to be considered for diagnostic, however did not mention the role of urodynamics such as PSA velocity for follow up and evaluation of treatment response

Response to comment 2: We appreciate the suggestion of incorporating urodynamics for follow-up and evaluation of treatment response. In Table 2 we state potential endpoints and define (amongst others) biochemical progression. We will collect all PSA values available throughout the course of the disease to determine treatment response per prostate cancer working group 3 criteria (PWG3), for which we will assess PSA decline (PSA>50% decline, PSA>90% decline and maximal PSA decline) and time to PSA progression, as biochemical response and progression endpoints

SAMPLING
Comment 3: The author described the selection procedure but the sampling technique was not stated i.e simple random sampling or convenient sampling

Response to comment 3: As we include (and select) all eligible patients in our retrospective cohort we do not use the reviewer's stated sampling techniques (i.e., simple random sampling or convenient sampling). We concur with the reviewer's observation that the title "sampling" lacks clarity and may lead to certain assumptions. Therefore, we changed the title sampling to patient identification (line 114-115 and line 143).

Comment 4: The sample size calculation is not clear , the author stated that the sample size was specified because of retrospective study design involvement , this reason does not suffice the justification, in my view the sample size specification for this design could not be deducted because the study intends to evaluate the overall data for de novo metastatic hormonal sensitive prostate cancer in Netherland for a specified time.

Response to comment 4: We sincerely appreciate this comment and have incorporated the suggestion of the reviewer in our manuscript (line 124-125 and 129-130).

TREATMENT STRATEGY
Comment 5: The author did not clarify how the randomization and blinding will be approached to optimize 75 for each interventional arm

Response to comment 5: The reviewer responded that we did not clarify how randomization and blinding will be performed. However, as our study is observational, we will not perform randomization and blinding for the treatment arms.

DATA COLLECTION
Comment 6: The author mentioned the source of data such as LOGEX , CTcue and IKNL tools , could you clarify how the reliability and validity of these tools were tested?

Response to comment 6: CTcue
We validated our own data query by comparing patient level data acquired from hospital records with data acquired from CTcue in two hospitals. During this validation we found all patient records relevant for data import and had therefore >90% concordance in the data. However, manual data collection was three times less time consumable with this AI tool compared to data collection directly from hospital records. Moreover, in a pilot study from the national castration resistant prostate cancer
registry (CAPRI), the validity and reliability of CTcue was prior tested and validated by high accuracy and reliability. The research team recently submitted a paper with their findings about this AI tool (manuscript under review).

IKNL
IKNL is an independent and well-established knowledge institute for oncological care in the Netherlands. IKNL facilitates nationwide identification of prostate cancer patients and professional data managers collect clinical data from patient records.

LOGEX
DBC-data must conform to several legal standards and is the basis for the reimbursement the hospital receives. It is therefore considered to be a highly reliable data source. LOGEX, a health analytics company, receives DBC data directly from the hospitals. Datasets are screened for missing and implausible values and validated against previous datasets from the same hospital. In case any validation checks fail, the hospital is contacted to provide an explanation and deliver an improved dataset if necessary.

QUESTIONNAIRES
Comment 7: The author described to evaluate the PROM using EORTC-C 30, EPIC-26, FACT-Taxane, BPI-SF, FACIT-Fatigue and FACT-Cognitive. The author did enumerate Taxane in the treatment strategy then why should the FACT-Taxane be employed?

Response to comment 7: The reviewer questioned whether the Taxane questionnaire should be employed for all patients, while Taxane treatment is only one of the possible treatment options. We agree that the FACT-Taxane is particularly interesting in patients receiving Taxane treatments such as Docetaxel, as this questionnaire specifically focuses on side effects and quality-of-life outcomes (HRQoL) that may be impacted by Taxane treatments. Nevertheless, for comparison, we also administered this questionnaire in patients without Taxane treatments to assess the Taxane specific interference on HRQoL. Lastly, from logistic reasoning, it is impossible to employ specific questionnaires for specific treatment options, as it is not known at inclusion which treatment will be initiated, or switched to, during the course of the protocol. All patients therefore receive the same questionnaires at the same time points.

Comment 8: In the eligibility criteria the authors mentioned to exclude all cognitive impaired patients on the other hand you intend to use the FACT-Cognitive to evaluate HRQoL this portends the data to high risk of bias (ROB) because majority of patients with the interest of outcome for QoL will be excluded.

Response to comment 8: We thank the reviewer for pointing out his/her concern. The main reason to exclude severe cognitive impaired patients is to improve validity of the questionnaires, as the questionnaires need to be filled in by patients themselves without help of others. Severe cognitive impairment at baseline (for instance due to dementia, mental impairment) would impact the quality of answers given in these questionnaires and therefore diminish validity. The amount of patients excluded based on severe cognitive impairment is deemed very minimal (e.g., 1-2 patients on 100 patients in total). Also, we think that the aim of the study, which studies longitudinal changes to evaluate how treatments impact cognition, does not introduce bias by excluding severe cognitive impaired patients at baseline. We choose this exclusion criteria due to the validity and quality of the given answers in the questionnaires. Nevertheless we agree that it would be of interest to understand what the cognitive changes are in patients with cognitive impairment, but the questionnaires in this study would not qualify to answer that given question. We have added more details on this exclusion criteria to our manuscript (line 138-141).
Comment 9: The author also mentioned to exclude patients who are not fluent Dutch speakers, however all the Questionnaires enumerated for assessment of QoL exist in English language can you clarify whether the validated Dutch language versions exist and if not how do you plan to translate and test them for reliability and validity?

Response to comment 9: We appreciate the reviewer’s valid concern on reliability an validity of the questionnaires used. All questionnaires were originally designed in English, yet all have been made available, and have been validated, in multiple languages including the Dutch language. Therefore, we did not need to translate them and test for reliability and validity. We chose to only send out one questionnaire (Dutch) and not for non-native speakers individualized questionnaires in their language of choice, as this would pose an impossible logistic task for the study to organize in 14 different hospitals. We understand that we might have a underrepresentation of non-native Dutch patients in this registry and will include this in our discussion.

ENDPOINTS
Comment 10: The author mentioned the primary endpoints as the QoL derived from the EORTC-QLQ-C30 score, however the time to event endpoints such as PFS and OS were not mentioned.

Response to comment 10: In table 2 potential endpoints with their definitions are written. In this table, you can find the survival endpoints (such as overall survival and progression-free survival). However, we agree with the reviewer, that because we wrote “retrospective cohort” in the text and title above, it was not clear that these endpoints and definitions apply for the total cohort. Therefore, we changed the word ‘retrospective’ to ‘total’ in our article (line 280 and 282).

Comment 11: On the data collection the author described how the cost variable as the outcome of interest collected by DBC, however it is not mentioned on this section.

Response to comment 11: In table 2 potential endpoints with their definitions are written. In this table, you can find the utilisation and costs. In accordance with our response to comment 10, we agree with the reviewer, that because we wrote “retrospective cohort” in the text and title above, it was not clear that these endpoints and definitions apply for the total cohort. Therefore, we changed the word ‘retrospective’ to ‘total’ in our article (line 280 and 282).

DATA ANALYSIS
Comment 12: The author did not explain how the cost effectiveness data is planned to be analyzed i.e Cost effectiveness Increment Ratio and Quadrant

Response to comment 12: We thank the reviewer for this comment and have added the planned descriptive analysis of costs to the paragraph on “Statistical analysis” (line 313-316). We do not intend to perform a cost-effectiveness analysis and therefore, did not incorporate the suggested cost effectiveness increment ratio and quadrant.

Reviewer 2:

We sincerely appreciate Reviewer 2 for the positive feedback on the significance of our work in the brief summary he/she provided.

In conclusion, we have taken all the reviewers’ comments into account, provided clarification on their queries in this rebuttal and have made suggested revisions to address their queries to improve the
We believe that the revised manuscript now meets the high standards set by BMJ Open. We kindly request you to reconsider our manuscript for publication in BMJ Open.

Thank you once again for the opportunity to revise and resubmit our manuscript. We appreciate your consideration and eagerly await your response.

VERSION 2 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Victor Kyaruzi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muhimbili University of Health and Allied Sciences, General Surgery</td>
<td></td>
</tr>
<tr>
<td>REVIEW RETURNED</td>
<td>06-Aug-2023</td>
</tr>
<tr>
<td>GENERAL COMMENTS</td>
<td>I congratulate the author for revising the manuscript accordingly</td>
</tr>
</tbody>
</table>