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

TITLE (PROVISIONAL)	Protocol for SNOTOB study: radical prostatectomy without prostate biopsy following 18F-PSMA-1007 PET/CT based on USTC diagnostic model: a single-center, single-arm, open-label study
AUTHORS	Wang, Changming; Dong, Qifei; Liu, Xuehan; Ni, Ming; Xie, Qiang; Xiao, Jun; Tao, Tao

VERSION 1 – REVIEW

REVIEWER	Debnath, Sashi The University of Texas Southwestern Medical Center, Radiology
REVIEW RETURNED	10-Jul-2023

GENERAL COMMENTS	Protocol for SNOTOB study: radical prostatectomy without prostate biopsy following 18F-PSMA-1007 PET/CT based on USTC diagnostic model: a single-center, single-arm, open-label study by Changming Wang and co-author presented a clinical protocol for radical prostatectomy for clinically significant prostate cancer (ClinicalTrials.gov Identifier: NCT05587192). Although this is a single-center, single-arm, open-label clinical study, the protocol is well-defined, and the intended accomplishments are well-projected. Additional explanations could be beneficial before publishing in BMJ Open. (1) Please briefly describe the radical prostatectomy method in this clinical protocol/trial. The follow-up plans after radical prostatectomy also need to be explained. (2) Any strategy behind the participant's number 57? Please describe. (3) Why the specific diagnosis with 18F-PSMA-1007 (positive result) is the inclusion criteria? Several other suitable clinically approved PET tracers are on the market, but 18F-PSMA-1007 has been selected for this study. Is tracer selection flexibility could be a constructive improvement? (4) Just curious about the terminology of the study ID "SNOTOB."

REVIEWER	Nordstrom, Tobias Karolinska Inst, Dpt Medical Epidemiology and Biostatistics
REVIEW RETURNED	30-Jul-2023

GENERAL COMMENTS	Thank you for the possibility to review this protocol. The authors aim to complete an ethically challenging study where men with very hogh risk of significant prostate cancer are offered radical prostatectomy without prior histological disease verification. The authors might consider some comments below:

	- From an ethical perspective, it is of highest priority to minimize the risk of performing surgery on men with (i) non-significant prostate cancer and (ii) men with significant prostate cancer but no clear indication for prostatectomy (e.g. men with comorbidities, high age etc). The protocol could be clearer how this is ensured. -The properties of the risk calculator and the PET could be clearer described incl the support for a sufficiently high PPV of the diagnostic chain to perform the propesctive trial. -The definition of significant disease is crucial. In contemporary prostate cancer treatment, also some men with intermeidate risk cancer might be treated with active surveillance. How does the authors secure that a reasonably low proportion of such men does not get unnecessary radical surgery? -In outcomes, it should be included a measurement of the proprotion of benign prostatectomies that are performed.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Dr. Sashi Debnath, The University of Texas Southwestern Medical Center
Comment 1
Please briefly describe the radical prostatectomy method in this clinical protocol/trial. The follow-up plans after radical prostatectomy also need to be explained.
Reply: Thank you very much for your valuable comment. We added the information of the radical prostatectomy method and the follow-up plans after radical prostatectomy and marked with red font. See
'Radical prostatectomy' section and 'Adverse events' section.

Comment 2
Any strategy behind the participant's number 57? Please describe.
Reply: Thank you very much for your comment. We are so sorry because we have described the participant's number in the 'Sample size' section. Do you mean we should provide a more detailed description?

Comment 3
Why the specific diagnosis with 18F-PSMA-1007 (positive result) is the inclusion criteria? Several other suitable clinically approved PET tracers are on the market, but 18F-PSMA-1007 has been selected for this study. Is tracer selection flexibility could be a constructive improvement?
Reply: The authors really thank you for your valuable and professional comment. Indeed, some PET tracers like 68Ga-PSMA-11 are more common in clinical practice. There are two main reasons why we choose 18F-PSMA-1007:
① Recently, two similar retrospective studies with small sample size adopted the 68Ga-PSMA-PET/CT (DOI: 10.1016/j.eururo.2021.11.019 and DOI: 10.12998/wjcc.v7.i12.1403). So, in this prospective and ethical support study, we select a new tracer 18F-PSMA-1007 and this tracer has longer physical half-life and can offer images of higher spatial resolution compare to 68Ga-PSMA.
② The 18F-PSMA-1007 PET/CT examinations in this study are free of charge for all enrolled patients and are funded by the research group. Due to limited funding budget, 18F-PSMA-1007 has the advantage of large-scale radiosynthesis, so it is more suitable for our needs.

Comment 4
Just curious about the terminology of the study ID "SNOTOB."

Reply: The study ID "SNOTOB" was provided by the corresponding authors. Which means say no to biopsy. We are very sorry that we forgot explain it in the manuscript. So, we added this information in the “Strengths and limitations of this study” section and marked with red font, Thank you very much.

Reviewer: 2 Dr. Tobias Nordstrom, Karolinska Inst
Comment 1
From an ethical perspective, it is of highest priority to minimize the risk of performing surgery on men with (i) non-significant prostate cancer and (ii) men with significant prostate cancer but no clear indication for prostatectomy (e.g. men with comorbidities, high age etc). The protocol could be clearer how this is ensured.
Reply: Thank you very much for your comment. In fact, this is one of the most discussed topics during the study design. First, patients without contraindications of radical prostatectomy was been set as an inclusion criteria in this study (see the 6th item of “Inclusion criteria” section). So, if patients with severe comorbidities like cardiopulmonary dysfunction, coagulation disorders or have no willing to accept radical prostatectomy will be excluded absolutely. Second, with the improvement of living level, Chinese people have longer life-span and we often can encounter patients over 80 years old strongly request radical prostatectomy even though they have been fully informed of the surgical risks and other alternative therapy methods. Third, although we have set a high cutoff value of the diagnostic model and further performed 18F-PSMA-1007 PET/CT examination to minimize the risk of performing surgery. But we still cannot guarantee that all enrolled patients will eventually be diagnosed with significant PCa. Actually, this is the mostly important observed outcome of this study. So, before the operation, patients and their family member will be fully informed of the surgical risks, the necessity to perform a prostate biopsy for pathologic confirmation, the possibility of benign prostatic disease and the other alternative therapy methods including active surveillance, radiotherapy, and focal therapies and so on. This information was written in detail in the Informed Consent Form. We also briefly described in the “Study design and setting” section and marked with red font. Thanks again!

Comment 2
The properties of the risk calculator and the PET could be clearer described incl the support for a sufficiently high PPV of the diagnostic chain to perform the propesctive trial
Reply: Thank you for your valuable advice, we can't agree with you more because our description of the risk calculator and the PET is too simple in the “Recruitment” section. We rewrite this paragraph and marked with red font, we hope you can be satisfied with our reply.

Comment 3
The definition of significant disease is crucial. In contemporary prostate cancer treatment, also some men with intermeidate risk cancer might be treated with active surveillance. How does the authors secure that a reasonably low proportion of such men does not get unnecessary radical surgery?
Reply: As you say, performing radical prostatectomy (RP) for patients with indolent prostate cancer or patients want to select other radical treatments is unbefitting. Therefore, patients' willingness to RP is an importantly assessed item before enrollment. Sometimes, the indolent prostate cancer is clinically insignificant, but it was significant in patient’s mind. Anyway, before the operation, patients and their family member will be fully informed of the surgical risks, the necessity to perform a prostate biopsy for pathologic confirmation, the possibility of benign prostatic disease and the other alternative therapy methods including active surveillance, radiotherapy, and focal therapies and so on. And patients can withdraw from the study at any time, even if they have already participated in the study. All these information was described in detail in the Informed Consent Form. we also submitted the informed consent form as a supplementary file according to editor’s request.

Comment 4

In outcomes, it should be included a measurement of the proprotion of benign prostatectomies that are performed.
Reply: Thank you for your comment. The measurement of benign prostatectomies is also very important, which means the misdiagnosis of PSMA combined model. We added a new secondary endpoint to calculate the misdiagnosis rate of our method, and also describe it in the “Statistical analysis” section. The revised content was marked with red font.

VERSION 2 – REVIEW

REVIEWER	Debnath, Sashi The University of Texas Southwestern Medical Center, Radiology
REVIEW RETURNED	09-Oct-2023

GENERAL COMMENTS	The modified article can be considered for publication.

REVIEWER	Nordstrom, Tobias Karolinska Inst, Dpt Medical Epidemiology and Biostatistics
REVIEW RETURNED	02-Oct-2023

GENERAL COMMENTS	Thank you for these answers and adjustment.