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)	Detection of ISUP≥2 Prostate Cancers Using Multiparametric MRI: Prospective Multicenter Assessment of the non-inferiority of an Artificial Intelligence System as compared to the PI-RADS Version 2.1 Score (CHANGE study)
AUTHORS	Rouvière, Olivier; Souchon, Rémi; Lartizien, Carole; Mansuy, Adeline; Magaud, Laurent; Colom, Matthieu; Dubreuil-Chambardel, Marine; Debeer, Sabine; Jaouen, Tristan; Duran, Audrey; Rippert, Pascal; Riche, Benjamin; Monini, Caterina; Vlaeminck-Guillem, Virginie; Haesebaert, Julie; Rabilloud, Muriel; Crouzet, Sébastien

VERSION 1 – REVIEW

REVIEWER	Norris, Joseph University College London, UCL Division of Surgery & Interventional Science
REVIEW RETURNED	05-Jun-2021

GENERAL COMMENTS	Thank you for inviting me to review this interesting protocol submission. The authors present a study protocol for a planned, exciting prospective trial to evaluate the use of mpMRI and AI for the detection of clinically significant prostate cancer (as defined by Gleason Grade Group 2, or above). I look forward to seeing the results of the full trial. I believe that this comprehensive trial protocol is worthy of publication, however, there are a few minor suggestions that may be addressed to improve the quality of this paper. Some specific point to address, include: - In this protocol, the authors provide a detailed description of how their planned trial will evaluate the simple biomarker, PHI. However, this is not mentioned in their title. I think that this should be added - especially, given that the authors have gone to the trouble to actually include the definition of significant disease in their title. - I also note that mention of PHI is absent from their hypotheses. - Clearly, the authors have gained full ethical approval for this planned trial - as expected. However, have they been granted specific ethics for the creation of their sharable/comparable CAD dataset? This may not be needed at this stage, and may only be warranted for future projects (which may need to apply for their own individual ethics approval), however, this aspect should be clarified, if possible.

	- The final bullet point in limitation section (after the abstract) should be more clearly stated (e.g. the CHANGE study is limited by...) - I note their is some intention to gather longitudinal data. How will this be done? Is this simply for subsequent diagnoses? Or will a more robust approach be taken to incorporate clinical outcomes (in which case HES data may provide the most reliable method)? - In description of their CAD methodology, the authors state that - "lesions of the transition zone with a complete peripheral capsule will be excluded from analysis regardless of their CAD score, since encapsulation is a definitive sign of benignity." This is problematic. By doing this, the authors are introducing a potential form of selection bias, and potentially erroneously decreasing the number of false positive cases detected by CAD. Can the proposed CAD system not account for well delineated BPH nodules? If not, then this should be strongly stated as a limitation (i.e. as a potential source of over-estimation on the diagnostic ability of CAD). - Will the authors consider including bpMRI? This could be done in a simple way - for example, considering mpMRI scores without DCE. - Will the authors use MCCL as part of their definition of clinical significance? If not, then it is not clear why this data is being collected. - On page 7, line 6 - do the authors mean "indication" instead of "cause"? - Will the authors account for PSAD? This is a simple radiological biomarker that has proved benefit in improving mpMRI risk stratification, however, it is absent in this submission. - It is unfortunate that no PPI was sought during the study design. - In the authors contribution section, it is stated that the authors "cooperated" with the study design. Perhaps, "contributed" would be more appropriate. - References 7 and 27 should be complete references and not hyperlinks. - In the study checklist section (page 20), in points 15/16 (i.e. handling of indeterminate/missing data), the authors state they have not included these details in the protocol, but will include them in their upcoming SAP. I don't quite know why these details need to be withheld until the SAP is written - they could easily be included in this protocol. However, perhaps this is best left to the discretion of the editorial team.

REVIEWER	Sarkis , Julien Hotel-Dieu De France
REVIEW RETURNED	20-Jun-2021

GENERAL COMMENTS	One of the strengths of this study is the three-year follow-up of patients, rarely seen in other mpMRI studies on prostate cancer.

	Detailing the characteristics of CAD used in the literature and the one that will be used in this trial is necessary. There are two types of CAD systems (Computer-aided detection (CADe) and Computer-aided diagnosis (CADx) systems). According to the protocol, a CADe system will be used in this study (i.e a system that provides parametric maps highlighting regions of the gland that may contain cancer). Some CAD systems have effectively been shown to improve human interpretation of multiparametric prostate MRI, but mostly in single-institution studies which makes it hard to extrapolate the results to other centers or MRI machines. In this multicenter trial, the external validity of the CAD system will be tested.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Mr. Joseph Norris, University College London
Comments to the Author:
Thank you for inviting me to review this interesting protocol submission. The authors present a study protocol for a planned, exciting prospective trial to evaluate the use of mpMRI and AI for the detection of clinically significant prostate cancer (as defined by Gleason Grade Group 2, or above). I look forward to seeing the results of the full trial. I believe that this comprehensive trial protocol is worthy of publication, however, there are a few minor suggestions that may be addressed to improve the quality of this paper. Some specific point to address, include:

R1.1. In this protocol, the authors provide a detailed description of how their planned trial will evaluate the simple biomarker, PHI. However, this is not mentioned in their title. I think that this should be added - especially, given that the authors have gone to the trouble to actually include the definition of significant disease in their title.
After careful analysis of the reviewer's comment, we have chosen not to include the PHI evaluation in the title. Indeed, the analysis of the potential impact of PHI on the diagnosis pathway is only an ancillary study. It was not considered for the calculation of the size of the study sample. In order not to complexify the title, we chose to only mention the study design and primary objective (see also answer to comment ED.2)

R1.2. I also note that mention of PHI is absent from their hypotheses.
We thank the reviewer for this comment. We mentioned PHI in the Research hypotheses paragraph.

R1.3. Clearly, the authors have gained full ethical approval for this planned trial - as expected. However, have they been granted specific ethics for the creation of their sharable/comparable CAD dataset? This may not be needed at this stage, and may only be warranted for future projects (which may need to apply for their own individual ethics approval), however, this aspect should be clarified, if possible.
This is indeed an important topic that has been extensively discussed with the legal department of the study sponsor (Hospices Civils de Lyon). The following sentence has been added in the document that the patients must sign: “Furthermore, unless you expressly object to the principal investigator/coordinator whose contact details appear on the first page of this document, your data collected in the context of this study may be transmitted elsewhere in the world and reused by public or private partners in subsequent research, exclusively for scientific purposes.”
Of course, all researchers who will seek access to the CHANGE dataset in the future will need to get their own individual ethics approval first.

We specified, in the Ethics and dissemination paragraph that patients also gave consent for the re-use of their data for subsequent research.

R1.4. The final bullet point in limitation section (after the abstract) should be more clearly stated (e.g. the CHANGE study is limited by...)
The fact that the final bullet point corresponds to a limitation of the study has been made clear.

R1.5. I note their is some intention to gather longitudinal data. How will this be done? Is this simply for subsequent diagnoses? Or will a more robust approach be taken to incorporate clinical outcomes (in which case HES data may provide the most reliable method)?
We thank the reviewer for this comment. The description of patient follow-up was not precise enough. We will record the date and type of treatment for all patients treated by active therapy for prostate cancer (prostatectomy, radiotherapy, brachytherapy, high-intensity focused ultrasound, hormone therapy, etc…) after the study biopsy. For patients with negative biopsy findings and for those managed by active surveillance, the date and results of any additional histological examination of prostate tissue (after additional prostate biopsy or transurethral prostate resection) will be recorded. Follow-up data will be collected from medical records or after a telephone interview with the patients. This is now specified in the Procedures paragraph.

R1.6. In description of their CAD methodology, the authors state that - "lesions of the transition zone with a complete peripheral capsule will be excluded from analysis regardless of their CAD score, since encapsulation is a definitive sign of benignity." This is problematic. By doing this, the authors are introducing a potential form of selection bias, and potentially erroneously decreasing the number of false positive cases detected by CAD. Can the proposed CAD system not account for well delineated BPH nodules? If not, then this should be strongly stated as a limitation (i.e. as a potential source of over-estimation on the diagnostic ability of CAD).
We do thank the reviewer for raising this issue. He is right and we modified the protocol according to his suggestion. The primary analysis will now focus solely on the raw results of the CAD. TZ nodules with a complete capsule will not be excluded from analysis. The corresponding sentence has been deleted.

R1.7. Will the authors consider including bpMRI? This could be done in a simple way - for example, considering mpMRI scores without DCE.
In the CHANGE trial, we will evaluate the best CAD system developed under the PERFUSE research program. This research program plans to develop CADs trained on mpMRIs and on bpMRIs. We hypothesized that the best algorithm would be developed on multi-parametric MRIs. Nonetheless, if the best algorithm turns out to have been trained only on bi-parametric datasets, the CHANGE cohort could be easily adapted. We will remove the DCE acquisitions from the test datasets, and the overall PI-RADS v2.1 score will be calculated without the DCE category, as detailed in the PI-RADS v2.1 guidelines. This is now briefly discussed in the Discussion section.

R1.8. Will the authors use MCCL as part of their definition of clinical significance? If not, then it is not clear why this data is being collected.
The definition of csPCa is currently highly controversial. Our primary objective will be assessed using the definition currently used in most studies (ISUP grade group ≥2). Nonetheless, we collected the ISUP grade group and the length of cancer invasion on a core-by-core basis, to be able to use alternate definitions for csPCa in the future, if this is needed.

R1.9. On page 7, line 6 - do the authors mean "indication" instead of "cause"?
Yes indeed, we meant “indication”. This has been corrected. Thank you.

R1.10. Will the authors account for PSAD? This is a simple radiological biomarker that has proved benefit in improving mpMRI risk stratification, however, it is absent in this submission.
Other simple biomarkers such as PSA density or PHI density can also be easily calculated from the database. Including them in combination with PHI and MRI would have resulted in too many possible diagnostic pathways, and we decided to include in the protocol only diagnostic pathways combining MRI and PHI.
A large body of literature is available on PSA density although the way it should be combined with MRI and the optimal diagnostic threshold remain unclear. Nonetheless, there may be guidelines for the use of PSA density when the inclusions are completed. Similarly, whether PHI density is useful is currently unclear, but this may be clarified at the end of the inclusions. If this is the case, the statistical analysis plan, written before the database is locked and can be accessed, may alter the tested diagnostic pathways and include PSA density and/or PHI density in these pathways. This is now discussed in the Discussion section.

R1.11. It is unfortunate that no PPI was sought during the study design.
We apologize, but this cannot be changed at this stage.

R1.12. In the authors contribution section, it is stated that the authors "cooperated" with the study design. Perhaps, "contributed" would be more appropriate.
Thank you for the comment. This has been corrected.

R1.13. References 7 and 27 should be complete references and not hyperlinks.
We checked all references.

R1.14. In the study checklist section (page 20), in points 15/16 (i.e. handling of indeterminate/missing data), the authors state they have not included these details in the protocol, but will include them in their upcoming SAP. I don't quite know why these details need to be withheld until the SAP is written - they could easily be included in this protocol. However, perhaps this is best left to the discretion of the editorial team.
Of course, we will do our best to reduce the number of indeterminate/missing data as much as possible. Nonetheless, there will probably be some. Patients for whom the principal objective cannot be assessed (e.g., missing MR images or biopsy findings) will be excluded as major deviations. The way the rest of indeterminate/missing data will be handled highly depends on their number and type. Therefore, we thought it was wise to wait until the statistical analysis plan is written to detail how these missing data will be handled. If the editor thinks we should specify this now, we are ready to do so and will welcome some guidance and suggestions.

Reviewer: 2
Dr. Julien Sarkis , Hotel-Dieu De France
Comments to the Author:

R2.1. One of the strengths of this study is the three-year follow-up of patients, rarely seen in other mpMRI studies on prostate cancer.
We thank the reviewer for his comment. This is indeed specified as a study strength in the “strengths and limitations of this study” bullet points.

R2.2. Detailing the characteristics of CAD used in the literature and the one that will be used in this trial is necessary. There are two types of CAD systems (Computer-aided detection (CADe) and Computer-aided diagnosis (CADx) systems). According to the protocol, a CADe system will be used in this study (i.e a system that provides parametric maps highlighting regions of the gland that may contain cancer).

We added in the Introduction section a brief description of the two types of CADs and specified that the goal of the PERFUSE research program is to develop CADe systems.

R2.3. Some CAD systems have effectively been shown to improve human interpretation of multiparametric prostate MRI, but mostly in single-institution studies which makes it hard to extrapolate the results to other centers or MRI machines. In this multicenter trial, the external validity of the CAD system will be tested.
This has been specified in the Introduction section.

VERSION 2 – REVIEW

REVIEWER	Norris, Joseph University College London, UCL Division of Surgery & Interventional Science
REVIEW RETURNED	12-Oct-2021

GENERAL COMMENTS	Thank you for the re-submission of your revised manuscript. Also, thank you for the systematic and thorough responses to my suggestions. On the whole, I agree that the revisions have been appropriate, and where rebuttals were given, these are all generally appropriate too. At this time, I have no further suggestions for improvement.