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) | Diagnostic Accuracy of CCTA-derived versus Angiography-derived Quantitative Flow Ratio (CAREER) Study: A prospective study protocol |
|---------------------|--------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Weng, Tingwen; Gan, Qian; Li, Zehang; Guan, Shaofeng; Han, Wenzheng; Zhai, Xinrong; Li, Ming; Qi, Lin; Li, Cheng; Chen, Yang; Zhang, Liang; Chang, Xifeng; Tu, Shengxian; QU, XINKAI |

VERSION 1 – REVIEW

| REVIEWER             | Evangelos Tzolos  |
|----------------------|-------------------|
|                      | The University of Edinburgh, BHF Centre for Cardiovascular Science |
| REVIEW RETURNED      | 25-Sep-2021       |
| GENERAL COMMENTS     | The authors are to be congratulated for the design of this important study that will for the first time describe the importance of non-invasively acquired QFR. I have no major concerns and I can only offer minor revision comments: |
|                      | Minor: General comment: Please maintain future tense throughout the manuscript when describing the future methodology. Rephrase manuscript accordingly i.e. "Coronary computed tomographic angiography is performed" to "Coronary computed tomographic angiography will be performed" ; "Coronary angiography is performed" to coronary angiography will be performed ; "All images are digitally stored" to "All images will be digitally stored" etc. |
|                      | Page 6, Row 17: Please rephrase "has not been studies" to "have not been studied". Page 10, Row 9: Correct "Coronary computed tomographic" to "Coronary computed tomography" |

| REVIEWER             | Anggoro Hartopo  |
|----------------------|-------------------|
|                      | Universitas Gadjah Mada, Cardiology and Vascular Medicine |
| REVIEW RETURNED      | 28-Sep-2021       |
| GENERAL COMMENTS     | Please give explanation about this questions: 1. " (2) invasive coronary angiography performed less than 30 days after CCTA", please explain why less than 30 days is selected . 2. Please explain the agreement tests between investigators assessing CT-FFR , QFR and FFR. 3. Does this research consider the comorbidites of subjects, such as diabetes mellitus, hypertension, chronic kidney disease, et cetera? |
Reviewer: 1:
Comment1: General comment: Please maintain future tense throughout the manuscript when describing the future methodology. Rephrase manuscript accordingly i.e. "Coronary computed tomographic angiography is performed" to "Coronary computed tomographic angiography will be performed"; "Coronary angiography is performed" to coronary angiography will be performed"; "All images are digitally stored" to "All images will be digitally stored" etc.
Response: Thank you for giving the valuable suggestion. We have rephrased our manuscript to maintain future tense when describing the future methodology. (Page 10, Row 3; Page 10, Row 8; Page 10, Row 16; Page 11, Row 9; Page 11, Row 12; Page 11, Row 13; Page 11, Row 16; Page 11, Row 20; Page 11, Row 22; Page 12, Row 1; Page 12, Row 2; Page 12, Row 5; Page 12, Row 6; Page 12, Row 13; Page 12, Row 12; Page 13, Row 4; Page 13, Row 15; Page 13, Row 18.)

Comment2: Page 6, Row 17: Please rephrase "has not been studied" to "have not been studied".
Page 10, Row 9: Correct "Coronary computed tomographic" to "Coronary computed tomography".
Response: We have rephrased our manuscript accordingly. (Page 6, Row 6; Page 10, Row 3.)

Reviewer: 2:
Major points
Comment: Comments to the Author
Please give explanation about this questions:
1. " (2) invasive coronary angiography performed less than 30 days after CCTA", please explain why less than 30 days is selected.
Response: Thanks for your question. In order to avoid a mismatch between CCTA images and invasive coronary angiography images due to the progression of the patient's coronary artery stenosis, we require that the enrolled patients must undergo coronary angiography within 30 days after CCTA. It will be more strict than undergoing coronary angiography within 60 days or longer time. In addition, many previous studies that have verified the diagnostic accuracy of CT-FFR have used 30 days as the interval between the CCTA and ICA[1, 2].

2. Please explain the agreement tests between investigators assessing CT-FFR , QFR and FFR.
Response: The investigators assessing CT-FFR, QFR and FFR have participated in training courses and obtained qualified certificates before the research as previously described in the Current Status section of the main text (Page 14, Row 1-4). More than fifty CAD subjects with various atherosclerosis features were included in the training courses and the invasive FFR was used as references standard to control the analysis results. The final exam included dozens of representative cases with invasive FFR as reference standard. Only those trainees who passed the final exams (with the diagnostic accuracy higher than 85% and the standard deviation of mean difference less than 0.05 between image-based FFR and invasive FFR) can get the training certificates, which can provide support for the agreement and consistence between different investigators. Furthermore, the investigators of this study have previously participated in prospective studies[3, 4] of angiography-based QFR, using FFR as the reference standard, which have already verified the agreement between different investigators.

3. Does this research consider the comorbidites of subjects, such as diabetes mellitus, hypertension, chronic kidney disease, et cetera?
Response: Thanks for the reviewer's valuable question. Patients with severe heart failure, who will not be suitable for ICA tests, and severe renal failure, which might induce incompatibility of contrast agents, will be excluded according to the exclusion criteria. However, patients with comorbidities such as diabetes mellitus, hypertension or other chronic diseases will not be excluded in this study. The fundamental mechanisms underlying the calculation of CT-QFR and QFR are the geometry reconstruction and the estimation of hyperemic boundary conditions. When the image quality and
hemodynamics will not be significantly influenced by these comorbidities, these subjects can be included with little influence on the results.