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)	Efficacy and safety of combination treatment of double plasma molecular adsorption system and low volume plasma exchange for patients with hepatitis b virus related acute-on-chronic liver failure, a multicenter randomized controlled clinical trial
AUTHORS	Xu, Wenxiong; Li, Yangmei; Wang, Lu; Gao, Hongbo; Chen, Jinjun; Yuan, Jing; Ouyang, Yi; Gao, Yufeng; Li, Jianguo; Li, Xuejun; Peng, Liang

VERSION 1 – REVIEW

REVIEWER	Fernandez-Rodriguez, Conrado Hospital Universitario Fundacion Alcorcon
REVIEW RETURNED	23-Jan-2021

GENERAL COMMENTS	This is the description of a multicenter, randomised non-blinded Phase II clinical trial undertaken in 6 Medical Centers in China addressing the efficacy and safety of a non-cellular extracorporeal device to treat HBV-related acute on chronic liver failure (ACLF). This condition has a high mortality and no specific treatment other than liver transplantation is currently available. The authors describe several methodological issues as sample size determination, randomisation method, inclusion and exclusion criteria, but I have been unable to find results. Major issues; 1. Results should be treated on an intention-to-treat (ITT) basis. Therefore, major side effects leading to stop treatment should be taken as a treatment failure. 2. MELD variation should be the second endpoint (bilirubin, creatinine and INR are described as end-point). 3. Range of MELD values should be specified in inclusion criteria. 4. The control group and the treatment active group received or will receive the best standard of care (SOC), it should be specified if this includes antiviral treatment (Tenofovir or Entecavir). 5. Informed consent should be translated into english for reviewer assessment. 6. Non-cellular is a preferable term instead of Non-bioartificial. Minor: 1. There is redundancy in information content in Methods and Analysis and Evolution and Outcomes sections.

REVIEWER	Larsen, Fin Stolze Rigshosp, Dept. of Hepatology
REVIEW RETURNED	04-Feb-2021

GENERAL COMMENTS	Nice and simple protocol. Is it correct that the patients will be in ACLF grade 1 or 2, not 3, i.e. with one or two organ failures only? Is it consecutive enrolled patients? Antiviral treatment? Any form of HD / RRT in spite normal kidney function?

VERSION 1 – AUTHOR RESPONSE

Comments from Reviewer 1:
1. Results should be treated on an intention-to-treat (ITT) basis. Therefore, major side effects leading to stop treatment should be taken as a treatment failure.
Answer: This comment has been added in the Evaluation and outcomes Section.

2. MELD variation should be the second endpoint (bilirubin, creatinine and INR are described as end-point).
Answer: We have changed the secondary efficacy outcome into MELD score variation in Abstract and in the Evaluation and outcomes Section in the main text.

3. Range of MELD values should be specified in inclusion criteria.
Answer: Firstly, HBV-ACLF patients in east Asia, especially in China, are quite different from ACLF patients in European and American countries. In China, half of the HBV-ACLF patients have no cirrhosis. We think MELD score system is not efficient to elevate the severity. Secondly, the trial recruits ACLF patients without other important organs dysfunction. The patients will be in ACLF grade 1 or 2, which are not in late stage of ACLF. As a result, we have not specified MELD values in inclusion criteria. Thank you.

4. The control group and the treatment active group received or will receive the best standard of care (SOC), it should be specified if this includes antiviral treatment (Tenofovir or Entecavir).
Answer: The treatment includes antiviral agents (Tenofovir or Entecavir). It has been added in the Interventions Section.

5. Informed consent should be translated into english for reviewer assessment.
Answer: We have uploaded an English version of Informed consent for reviewer assessment.

6. Non-cellular is a preferable term instead of Non-bioartificial.
Answer: This has been corrected in the main text.

7. There is redundancy in information content in Methods and Analysis and Evolution and Outcomes sections.
Answer: Some contents have been shortened.

Comments from Reviewer 2:
1. Is it correct that the patients will be in ACLF grade 1 or 2, not 3, i.e. with one or two organ failures only?
Answer: The trial recruits ACLF patients without other important organs dysfunction. So, it is correct that the patients will be in ACLF grade 1 or 2.

2. Is it consecutive enrolled patients?
Answer: Yes. The trial enrolls patients consecutively if they meet eligibility criteria.

3. Antiviral treatment?
Answer: The treatment includes antiviral agents (Tenofovir or Entecavir). It has been added in the Interventions Section.

4. Any form of HD / RRT in spite normal kidney function?
Answer: The interventions in trial group of this trail include double plasma molecular adsorption system (DPMAS) and plasma exchange (PE). HD / RRT are not included in this trial.