PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Letrozole, Berberine, or Their Combination for Anovulatory Infertility in women with Polycystic Ovary Syndrome: Study Design of a Double-blind Randomized Controlled Trial
AUTHORS	Li, Yan; Kuang, Hongying; Shen, Wenjuan; Ma, Hongli; Zhang, Yuehui; Stener-Victorin, Elisabet; Ng, Ernest; Liu, Jianping; Kuang, Haixue; Hou, Lihui; Xiaoke, Wu

VERSION 1 - REVIEW

REVIEWER	Bob Silver University of Utah, U.S.A.
REVIEW RETURNED	30-Sep-2013

GENERAL COMMENTS	This is a methods paper describing a randomized clinical trial comparing letrozole, berberine, or both to treat anovulatory infertility on women with PCOS. Berberine is in widespread use in traditional Chinese medicine. However, it has not been extensively studied in the treatment of women with PCOS. The study is clinically relevant and of interest to readers of the journal. Much current fertility practice is not evidence based and high quality data from appropriately designed RCTs are lacking. This is especially true for traditional Chinese medicines. These studies are difficult to conduct making a methods paper useful for other investigators. In addition, the paper is likely to be highly cited by the team of investigators upon completion of the trial. Questions and suggestions for enhancing this manuscript include: 1. The paper is well organized and well written. However, the language requires a bit of editing. 2. It would be good to precisely define secondary outcomes. 3. A table with the protocol (i.e. visits, etc.) should be included. 4. A timeline should be included. 5. Are the glucose and / or insulin levels to be assessed while women are fasting? 6. Is there a method to assess compliance? 7. The sample size calculation should include alpha and beta error.

REVIEWER	Dr Marie Misso Head of the Evidence Synthesis Program Monash Centre for Health Research and Implementation - MCHRI, School Public Health and Preventive Medicine Monash University - in partnership with Monash Health Australia
REVIEW RETURNED	01-Oct-2013

GENERAL COMMENTS	A novel, clinically important and well planned trial with steps to

	minimise bias - I look forward to the results.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Bob Silver
Institution and Country, University of Utah, U.S.A.
Please state any competing interests or state 'None declared':None declared.

This is a methods paper describing a randomized clinical trial comparing letrozole, berberine, or both to treat anovulatory infertility on women with PCOS. Berberine is in widespread use in traditional Chinese medicine. However, it has not been extensively studied in the treatment of women with PCOS. The study is clinically relevant and of interest to readers of the journal. Much current fertility practice is not evidence based and high quality data from appropriately designed RCTs are lacking. This is especially true for traditional Chinese medicines. These studies are difficult to conduct making a methods paper useful for other investigators. In addition, the paper is likely to be highly cited by the team of investigators upon completion of the trial. Questions and suggestions for enhancing this manuscript include:

1.The paper is well organized and well written. However, the language requires a bit of editing.

Answer: We proof the manuscript and made some changes.

2.It would be good to precisely define secondary outcomes.

Answer: Thank you for your suggestion, we have detailed the secondary outcomes.

3.A table with the protocol (i.e. visits, etc.) should be included.

Answer: The table of the study visits was attached at the very end of the manuscript.

4.A timeline should be included.
Yes at Pg 9.

5.Are the glucose and / or insulin levels to be assessed while women are fasting?

Answer: Yes, and we clarified that in the manuscript.

6.Is there a method to assess compliance?

Answer: The patients are required to bring back the left drug, empty bottle and packs during every visit so the coordinator could check if they took the study drug per protocol.

7. The sample size calculation should include alpha and beta error.

Answer: Thank you for the reminder, $\alpha = 0.05$, $\beta = 0.1$, we've added this in the sample size calculation part.

Reviewer Name Dr Marie Misso
Institution and Country Head of the Evidence Synthesis Program
Monash Centre for Health Research and Implementation - MCHRI,
School Public Health and Preventive Medicine

Monash University - in partnership with Monash Health
Australia
Please state any competing interests or state ‘None declared’: None declared

Please note that I do not have statistical expertise and thus have selected 'yes' above.