Reviewer’s report

**Title:** Safety and Tolerability of Experimental Hookworm Infection in Humans with Metabolic Disease: Study Protocol for a Phase 1b Randomised Controlled Clinical Trial

**Version:** 1  **Date:** 02 Aug 2019

**Reviewer:** Reviewer 2

**Reviewer's report:**

"PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses one or several testable research questions? (Brief or other article types: is there a clear objective?)
Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with sufficient technical rigor to allow confidence in the results?
N/A - no experiments or analyses

STATISTICS - Is the use of statistics in the manuscript appropriate?
N/A - there are no statistics in this study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?
N/A - no results to interpret

OVERALL MANUSCRIPT POTENTIAL - Has the author addressed your concerns sufficiently for you to now recommend the work as a technically sound contribution? If not, can further revisions be made to make the work technically sound?
Probably - with minor revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: The authors have clearly attended to all the comments made by previous reviewers. They have provided justification for optional anthelmintic treatment after the end of the study. However, in view of the ethical issues surrounding this type of study, it will be good that the participants are very much aware of the implication of having hookworm infection during the duration of the study.
REQUESTED REVISIONS:
Authors should emphasize that anthelmintic treatment after the study is mandatory. Therefore, offering the optional anthelmintic treatment is not acceptable as the study participants can become a source of contamination which lead to the establishment of Necator Americanus in Australia. Inoculation of 20-40 third stage larvae are enough to establish a serious hookworm disease in any non-exposed human. I surprised this protocol was approved.

ADDITIONAL REQUESTS/SUGGESTIONS:
The author should revise the protocol to make it mandatory for all study participants receive anthelmintic treatment. The option of keeping the helminths is not acceptable, even if the trial is successful. "

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.
Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.
Unable to assess

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.
Not relevant to this manuscript

Quality of written English
Please indicate the quality of language in the manuscript:
Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:
1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

This reviewer has been recruited by a partner organization, Research Square. Reviewers with declared or apparent competing interests are not utilized for these reviews. This reviewer has agreed to publication of their comments online under a Creative Commons Attribution License attributed to Research Square and was paid a small honorarium for completing the review within a specified timeframe. Honoraria for reviews such as this are paid regardless of the reviewer recommendation.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal