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

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Reviewer: Kalyan Goswami

Reviewer's report:

The manuscript entitled 'Safety and Tolerability of Experimental Hookworm Infection in Humans with Metabolic Disease: Study Protocol for a Phase 1b Randomised Controlled Clinical Trial' appeared to be relevant work. However, since it is a protocol only, so it has less practical standing based on any actual result. On reviewing the proposed protocol, it appeared that there are several issues which needs justifiable treatment as also this plan seems very sketchy.

First in the design justification for not doing a cross over design must be considered. Since this study is based on worm therapy and associated immunological aspect, therefore it is imperative that the history of parasitic infection of the study participants should be a major recruitment criterion. However that was not mentioned. Also it is important to have idea of the place of residence of these subjects which pertains to endemic normal status of the individual, if they belong to any area where the parasite is naturally endemic. Also whether during the course of the study if any pregnancy occurs, how it will be dealt with, must be mentioned, not only screening at the onset of the study will suffice.

It was mentioned that the mandatory requirement for the study participants to 'purchase' the antihelminthic medication, which seems objectionable as it is the moral /ethical responsibility of the investigator to provide rather than asking to 'purchase'. It's also quite contradictory to mention in the next sentence that 'however, it is not mandatory for participants to comply with this direction!' If it is a mandatory requirement then how it is not mandatory for the participants to follow that direction? Moreover, it is also very difficult to accept that ‘Participants electing to keep their helminths will be advised that their future medical care is their own responsibility.' Since the study is still continuing (even it is optional for the participants) after 2 years, then the benefit of this follow-up is added onto the study results and will enrich the data, therefore it is unethical to discontinue the provision for medical care, leaving that as their responsibility.

The study variables has not been mentioned very clearly and a broad outline only is provided, which makes the protocol weak. How the meta-genomic profile of microbiome will be linked to the parasitic effect on Metabolic syndrome has to be explained with justification. Specific immunological markers also need to be spelt out.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

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