Author's response to reviews

Title: Target disease-guided placebo control (TIGER) design -- A Novel Method for Acupuncture Clinical Trials

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Dear TRIAL editors and reviewers,

Thank you very much for your comments on the manuscript named “Target disease-guided placebo control (TIGER) design—A Novel Method for Acupuncture Clinical Trials”. We are now submitting the revised manuscript.

We have made revisions according to your valuable comments and will give explanations point-by-point in the following text.

1.1 We propose the hypothesis that the overall therapeutic effect of acupuncture is a combination of the real effect (specific effect) and the placebo effect. Although unsupported, we also propose that the patients’ psychological factors contribute the most to the placebo effects. Using adequate design, it is possible to measure the real acupuncture effect and placebo effect separately.

1.2 The placebo effect of acupuncture originates from a number of individual, context and cultural factors. There are studies examining the components of acupuncture placebo effects, but this field of research is under studied thus far. Despite this, we believe the most important factor is psychological factors and used it to cover all the other factors related to the placebo effect.

1.3 Participants suffering simultaneously from the target disease and the pseudo-target disease will be recruited. This is our inclusion criteria. For instance, in our planned trial of acupuncture for migraine, participants having migraine and constipation at the same time will be included.

1.4 In the example of acupuncture for migraine, patients in Arm One were informed that they would receive acupuncture therapy for migraine, while patients in Arm Two were told they would receive acupuncture for constipation. We believe the results of Arm One showed both the acupuncture real effects and the placebo effects, while the results of Arm Two showed only the acupuncture real effects. In other words, acupuncture real effects can be reflected by the changes in Arm Two patients. The placebo effect can be calculated using the results of Arm One patients minus those of Arm Two patients using an adequate statistical model.

1.5 We have made a more detailed flow chart and explained more clearly.

1.6 “The acupuncture therapeutic effect is a combination of the real treatment effect and the placebo effects (psychological effects).” We have a reference supporting this statement. In Paterson et al.’s paper "characteristic and incidental (placebo) effects in complex interventions such as acupuncture", the authors distinguished between the characteristic (specific) and incidental (placebo) effects of the
acupuncture therapy as components of the total therapeutic effect.

1.7 We developed the **TIGER** method to examine the net specific effects of needling treatment and the placebo effects respectively.

As a new method, there are some limitations: 1. The new control design needs to be tested for feasibility in clinical trials for a variety of diseases. 2. The use of this control design required the patients to have both the target disease and the pseudo-target disease. Therefore, recruiting qualified patients can be challenging. 3. The external validity of the results is invariably affected as subjects included were highly selective. In another word, research findings from patients suffering from a combination of conditions may not be applicable in the general patient population.

2.1 We have checked the language carefully.

Sincerely,

Wenke Zheng