Author's response to reviews

Title: Efficacy of Modified Liujunzi decoction on functional dyspepsia of spleen-deficiency and qi-stagnation syndrome A randomized controlled trial

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Author's response to reviews: see over
Dear editor,

Thank you for your time and efforts. According to the editors’s comments on our manuscript, we have finished a point-by-point response and revised in the manuscript. We hope that the response is acceptable. If there are still some questions which was not explained clearly, then please do not hesitate to contact me.

**Question 1: Why did the authors use a 2:1 randomization plan?**

**Response:** For the placebo-controlled trials it was ethically desirable to have more subjects in treatment group compared to placebo group. For the trial with ill subjects it was unethical to assign equal subjects to each arm. In order to protecting subjects’ right, we used a 2:1 randomization plan.

**Question 2: Were the sample sizes based on the outcome scores that were used in the study?**

**Response:** There was no previous studies based on the outcome scores in this trial, so some value in the formulas of calculating sample size was estimate conservatively according to our clinical experience. We performed sample size calculations in two ways. Method 1 was described in the manuscript \( (N_1=106, N_2=54) \), the other method will be represented below \( (N_1=84, N_2=42) \). In order to guarantee the reliability of the trial, the larger sample size was used.

Method 2:

Formula of calculating sample size is
\[ n = \left( Z_{\alpha} + Z_{1-\beta} \right)^2 \times \{2(\delta)^2\}/(\mu_1 - \mu_2)^2 \]

where

Level of significance = 5%, Power = 80%, Type of test = one-sided

\( n \) = sample size required in each group,

\( \mu_1 \) = mean change in TDS score from baseline to week 4 in CHM = 4,

\( \mu_2 \) = mean change in TDS score from baseline to week 4 in placebo = 2.5,

\( \mu_1 - \mu_2 \) = clinically significant difference = 1.5

\( \delta \) = standard deviation = 2.5

\( Z_{\alpha} \): This depends on level of significance, for 5% this is 1.64

\( Z_{1-\beta} \): This depends on power, for 80% this is 1.28

If \( n \) is sample size required as per formula and \( n_1 \) is the sample size for test and \( n_2 \) is sample size for placebo and \( k = n_1/n_2 = 2 \), then

\[ n_1 = (0.5) \times n \times (1 + k) = 72 \]

\[ n_2 = (0.5) \times n \times (1 + (1/k)) = 36 \]

If \( n \) is the sample size required as per formula and if \( d \) is the dropout rate then adjusted sample size \( N \) is obtained as:

\( d = 15\% \)

\[ N_1 = n_1 / (1-d) = 84 \]

\[ N_2 = n_2 / (1-d) = 42 \]

**Question 3: Were the outcome measures validated?**

**Response:** Yes, the outcome measures were validated. There was two primary Outcomes in this trial Total dyspepsia symptom scale (TDS) and Single dyspepsia symptom scale (SDS). TDS was modified from Global Overall Symptom (GOS) scale which had previously been used as an outcome measure in studies evaluating FD[1,2]. SDS was part of the Nepean Dyspepsia Index (NDI). Since the development of NDI in 1998[3], it has been used as an outcome assessment in many FD clinical researches[4,5] and translated into several languages.


**Question 4:** Were the results clinically meaningful?

**Response:** Yes, the results were clinically meaningful. According to the clinically evaluation criterion of symptoms (below), the clinical global impression of improvement rating at post-treatment showed the following significant results for the treatment group vs. placebo group: very much improved (50.9% vs. 18.5%), much improved (22.6% vs. 29.6%), small improvement (18.9% vs. 14.8%), unchanged or deterioration (7.5% vs. 37.0%) (chi-2= 26.559; p<0.001).

Clinically evaluation criterion of symptoms:
Meliorative percentage = (TDS scores before-treatment - TDS scores post-treatment) / TDS scores before-treatment *100%
very much improved: Meliorative percentage ≥75%
much improved: $51% \leq \text{Meliorative percentage} < 75$
small improvement: $25% \leq \text{Meliorative percentage} < 50$
unchanged or deterioration: $\text{Meliorative percentage} < 25$

**Question 5:** How did you verify that clinicians remained blinded to study group assignment?

**Response:** Randomisation was performed with a computer-generated program. Eligible patients were assigned a randomisation number according to a predetermined list at each centre. These numbers were allocated in sequential order and registered in the patient enrolment list and the allocation was concealed. Emergency envelopes containing the randomisation code were provided to the investigators and were examined at the end of the trial to ensure that the trial blinding had been maintained.

Thank you again for your cooperation.

Sincerely yours,

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