Author's response to reviews

**Title:** Effect of sequential treatment with syndrome differentiation on acute exacerbation of chronic obstructive pulmonary disease and "AECOPD Risk-Window" : a randomized placebo-controlled study

**Authors:**

- Wang Haifeng (wangh_f@126.com)
- Li Jiansheng (li_is8@163.com)
- Li Suyun (lisuyun2000@yahoo.com.cn)
- Yu Xueqing (yxgshi@126.com)
- Zhang Hailong (zhanghailong6@126.com)
- Wang Zhiwan (zhiwan_w@163.com)
- Wu Qiyi (wuqiyi1997@126.com)
- Zhang Pankui (zhangpankui@126.com)
- Wang Zhongchao (geianna@126.com)
- Li Fenglei (leifeng0217@126.com)
- Yan Haihong (yhh5858@126.com)

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Dear prof. Editors-in-Chief: Doug Altman, Curt Furberg, Jeremy Grimshaw and Peter Rothwell

/Editor-in-chief

My manuscript entitled as “Effect of sequential treatment with syndrome differentiation on acute exacerbation of chronic obstructive pulmonary disease and"AECOPD Risk-Window": a randomized placebo-controlled study” was revised according to the reviewer’s comments, and itemized response to the reviewer’s comments is attached. Many thanks for your suggestion. I am sorry to bring you so much trouble because of our careless. Correspondence and phone calls about this paper should be directed to prof. Jiansheng Li at the following address, phone and fax number, and e-mail address:

Institute: Henan University of Traditional Chinese Medicine,

Adress: No.1 Jinshui Road Zhengzhou Henan PR China

Tel: 86-371-65676568

Fax: 86-371-65680028

E-mail: li_js8@163.com

Thanks very much again for your attention to our paper. Once again, thank you for your help to our paper processing. I hope this paper is suitable for your famous journal.

Yours sincerely,

Li Jiansheng
For your guidance, itemized response to each reviewer’s comments is appended below.

Dear reviewer:

1. As suggest by the reviewer, “the manuscript should be paginated.” we have paginated the paper. (see page footer, Page 1-14).

2. Since the reviewer has point out that “The Abstract Methods and Design says the study is double blind, whereas elsewhere it is said to be single blind.” I am so sorry for my careless, in the abstract part I made a mistake, the study is single blind. (see line 14 from top, Page 2).

3. The reviewer has point out that “Several abbreviations need to be spelled out before being used (eg, AECOPD, WHO/NHLBI/GOLD, MMRC).”, we thank the reviewer’s carefulness, and we defined abbreviations when first used and a list of abbreviations be provided following the main manuscript text. (see line 6, 10, 21 from top, Page 2, and line 13, 17-18 in Page 3, and line 23 in Page 8.)

4. As the reviewer has point out that “The study is said to be conducted in 8 hospitals but 4 sites. That needs to be clarified.”, It is because subjects be enrolled at eight hospitals: 1) The first affiliated hospital of Henan university of TCM; 2) TCM hospital of Xinjiang uygar autonomous regeion; 3) Sichuan province TCM hospital; 4) Jiangsu province hospital of TCM; 5) The first affiliated hospital of Henan university of science and technology; 6) Henan university of huaihe hospital; 7) The first affiliated hospital of zhengzhou university; 8) Henan provincial chest hospital.
In the 8 hospital, 4 of them (the first affiliated hospital of Henan university of TCM, Henan university of huaihe hospital, The first affiliated hospital of zhengzhou university and Henan provincial chest hospital) are in Henan province in PR China, the other 3 are in Sichuan province, Jiangsu province and Xinjiang uygur autonomous region, so we said the study is conducted in 4 sites in China.

5. According to the reviewer’s advise, “the traditional Chinese medicine should be described”, There are 3 TCM formula for exacerbation will be administered orally for 7-21 days, they are sanhanhuayinfang (Ephedra, Rumulus Ginnamomi, Rhizoma Zingiberis, ect), qingrehuatanfang (mongolian snakegourd fruit, Rhizoma Pinelliae, Bulbus Fritillariae Cirrhosae, ect), zaoshihuatanfang (Prepared Pinellia Tuber, Officinal Magnolia Bark, Tangerine Peel, ect), There are also 3 TCM formula for AECOPD-RW will be administered orally for 4 weeks, they are bufeijianpifang (Codonopsis, Astragalus root, Largehead Atractylodes Rhizome, Perilla Fruit, Mangnolia officinalis, ect), bufeiyishenfang (Ginseng, Astragalus root, medlar, ect), yiqizishenfang (Ginseng, solomonseal, Rehmannia Glutinosa, ect). all drug were made into granules by Jiangyin Tianjiang Pharmaceutical Co., Ltd.(see line 13-22 in Page 6)

6. As the reviewer has point out that “blocks of 4”, I am so sorry that I have made a mistake in here in writting the paper, the study use central randomization system, randomization lists will be computer-generated. No one knows the blocks. (the randomization web page: http://www.gztcmgcp.net/sjxt/login.asp).

7. Since the reviewer has point out that “How much drop-out, lost-to-follow-up, missing data, etc is expected and were those taken into account in the sample size determination”, we have taken into account in the sample size about the drop-out and
lost-to-follow-up, it is estimate about 20% dropout rate over the course of the study, 182 patients will be enrolled in each group. The total sample size will be 364. (see line 23-24 in Page 7)

8. As the reviewer has point out that “The sample size was determined for the primary outcome of change in clinical symptoms. But what about the other “primary outcomes” of MMRC scale and exacerbations? Is the sample size adequate for those?”

There are seldom study of traditional Chinese medicine for acute exacerbation of COPD and most of them published in China, symptoms and signs are usually selected as the primary outcomes in china, other outcomes are rare used. MMRC scale and exacerbations are used regular as primary outcomes in many important clinical research. In our study, The sample size can only be determined by change of clinical symptoms, but we want to investigate the change of MMRC scale and exacerbations, so both of them were selected as the primary outcomes too.

As a Chinese, our English is very poor and a few of corrections and editing had done by our team. At last, thank you for your arduous work and instructive advice.