Reviewer's report

Title: Acupressure Therapy and Liu-Zi-Jue Qigong for Pulmonary Function and Quality of Life in Patients with Severe Novel Coronavirus Pneumonia (COVID-19): study protocol for a randomized controlled trial

Version: 1 Date: 16 Jun 2020

Reviewer: Alexander Gough

Reviewer's report:

SPIRIT checklist review for Revision 1 TRLS-D-20-00232R1
Thank you for your revisions. There are a few minor points that are outstanding, listed below in conjunction with the original review and author responses.

Original review and comments:
1. This is a timely trial as it is important to find adjunctive treatments for this condition. There are a number of specific comments about the trial protocol that need addressing which are listed below. More generally, the manuscript needs extensive revision by an English speaker for language. In most places where there are errors, the meaning is clear, but the grammar or spelling is incorrect. In some places however, the errors make the meaning unclear. Response: Yes, we have asked native English-speaking editors to make language changes to the manuscript.

There is still some language editing required for clarity

2b It is recommended to include a table of WHO organization Trial Registration Data Set in the manuscript. Response: We have added an Additional file 3 as the table of WHO organization Trial Registration Data Set in the manuscript. However, I don't quite understand the content, so I look forward to the reviewers to give corresponding comments. This seems fine, thank you.

5b Please specify the name and contact information for the trial sponsor. Response: For COVID-19, the trial sponsor are the Shanghai Municipal Government and Shanghai University of Traditional Chinese Medicine. The final fund management is performed by the Yueyang Integrated Traditional Chinese and Western Medicine Hospital affiliated to Shanghai University of Traditional Chinese Medicine. The public contact email is yykyc2004@163.com.

Please include the name of the sponsor in the manuscript

5c Please specify the role of the sponsor if applicable Response: The funders had no role in the design of the study, analysis, collection, and interpretation of the data, or the writing and decision for publication of the manuscript. All these funding is a wider group of projects and apply to this study. Thank you

6b Please explain the choice of comparator - why did you choose standard therapy? Response: For the emergency event of COVID-19, standard therapy is a standard therapy developed in strict
accordance with the National Diagnostic and Treatment Protocol for Novel Coronavirus Pneumonia (The 7th Trial Version). For patients, standard therapy is necessary to prevent death and other adverse consequences.

Thank you

7 Could you clarify what you mean by your second research question on page 6. Response: I have modified the research question and turned it into a hypothesis. We make a hypothesis that official conventional therapy plus TCMR has better clinical efficacy than single conventional therapy on clinical symptoms, mental health and quality of life.

Thank you

8 Please confirm this is a superiority trial. Response: This is a single-center, parallel-arms, superiority randomized controlled trial (RCT).

Thank you

11c Please describe strategy for monitoring adherence to the intervention, especially the Liu-zi-jue Qigong. Response: The nurse informs the patient to perform Liu-zi-jue exercise every day at 9 am and 4 pm. Each ward of the subject has remote monitoring so that the remote monitoring of the training of the subject can be achieved, and the participants are required to sign in as a diary after each exercise. Eventually, participants who can complete the training will be rewarded with monetary rewards.

Thank you

14 Could you clarify the clinical assumptions in arriving at your sample size? What level of improvement were you looking for to get this result? Response: PASS software (PASS 11. NCSS, LLC. Kaysville, Utah, USA) will be used to estimate the sample size utilizing two independent sample means ($\alpha = 0.05$, $\beta = 0.10$). We will use the mMRC as the primary efficacy outcome. Based on previous clinical studies on the effect of respiratory symptoms after acupressure therapy plus Liu Zi Jue Qigong interventions, the mMRC scale score in the control group is 0.52 with a standard deviation of 0.11, and the average mMRC scale score in the treatment group is 0.95 with a standard deviation of 0.92. In this study, the target sample size will be 72 participants, anticipating on maximum loss to follow up of 20%.

Thank you

16c Please clarify who will enroll participants. Response: The informed consent process was conducted by the principal investigator (LF) or study coordinator (WC) which will screen participants to confirm that potential participants meet the eligibility criteria listed below if the participants agree to sign the informed consent.

Thank you

18a If possible, please provide data on the reliability and validity of the MDS and ADL primary outcome measures. Please provide data collection forms or refer to where they can be found. Response: Modified Medical Research Council (mMRC) dyspnea scale and Activities of Daily Living Barthel Index (ADL-BI) Scale were used as the primary and secondary outcome measurements. They were widely used to evaluate the dyspnea symptoms and activities of daily living, which has been proved with good reliability and validity in the trials.
Thank you. Could you provide data collection forms or refer to where they can be found, I couldn't see them in the revised manuscript.

18b Please detail any plans to promote participant retention. Response: An adequate retention plan is a valuable component of the research design process that can enhance participants' ties with the researchers and the study. First, we will establish a local retention working group including the research coordinator and nurses. The coordinator and nurse will be fully trained before the trial starts; by focusing on daily communication strategies, they can improve retention after receiving additional attention. Furthermore, it is useful to provide sufficient funds within the study budget to compensate the nurses and participants for retention. Subjects will be monitored from a distance while completing their daily physical therapy with a diary recording.

Thank you

19 Please list any measures to promote data security and how it will be stored. Response: The administrators in Science and Technology Department of SUTCM will be responsible for monitoring the data management. The test data is recorded on the sub website of China Clinical Trial Center (http://www.medresman.org.cn/login.aspx) electronic data management system. Paper CRFs will be designed to collect test data according to the trial protocol, which will be stored in a securely locked location. We will conduct a double independent data entry to promote the data quality, then locked and analyzed it by an independent statistician under the supervision of the principle investigator. Electronic database will be closed after data entry is completed.

Thank you

20c Please explicitly describe which participants will be included in the main analyses and define the study group in which they will be analyzed (e.g. as randomized). Response: All main analyses will be carried out at the three-time points assessments between two groups and will be based on the intention-to-treat principle.

Thank you

21a Please declare the data administrator in the Science and Technology Department is independent and how they will report. Response: The administrators at the Science and Technology Department of SUTCM will be responsible for monitoring data management as an independent third party. Paper Case Report Forms (CRFs) will be designed to collect test data according to the trial protocol, which will be stored in a securely locked location. We will conduct double independent data entry to promote data quality. Then, it will be locked and analyzed by an independent statistician under the supervision of the administrators. The test data will be recorded on the sub website of China Clinical Trial Center (http://www.medresman.org.cn/login.aspx) electronic data management system. The electronic database will be closed after data entry is completed.

Thank you. Could you provide more details on how the administrators will report their findings on data monitoring.

21b Please describe any interim analyses planned. Response: Interim analysis will not be conducted.

Thank you

25 Please give more detail on plans to communicate important protocol modifications to relevant parties. Response: If necessary, researchers can submit a request to modify the protocol for
example the primary outcome and sample size calculation. And the steering committee and ethics committee have the authority to allow the modification of the plan.

Thank you. How would those changes be communicated to the relevant parties?

29 Please state why availability of data and materials is not applicable in this study. Response: It does not contain any data in the protocol manuscript, so I declare that data and materials is not applicable in this study.

Thank you

30 Please give more detail in the manuscript about provisions for patients who suffer harm during the trial. Response: Regardless of the cause, if the condition suddenly worsens during the trial and is accompanied by severe complications or serious adverse reactions, the trial will be terminated immediately, and prompt medical measures will be taken according to the subject's condition. The specialist will be prepared to deal with some harm during the study at any time, with treatments including oxygen therapy support, venous access and reasonable medication to maintain normal vital signs.

Thank you

31b Please clarify which authors will be eligible to be included as authors on the final trial report, and whether any professional writers will be utilized. Response: Shuaipan Zhang, Qingguang Zhu, Chao Zhan, Wei Cheng, Xiao Ming fang, Min Fang, Lei Fang are eligible to be included as authors on the final trial report and no professional writers will be utilized.

Thank you

31c Please state any plans for public access to the protocol, dataset and code. Response: The datasets generated and analyzed during the study will be available in the [Fig share] repository.

Thank you

32 Please supply a model consent from as part of the manuscript or an additional document. Response: I have provided Additional file 2 as a model consent from.

Thank you

33 Please give more detail on the collection, laboratory evaluation and storage of biological specimens for possible future use. Response: There is no collection, laboratory evaluation and storage of biological specimens.

Thank you

Level of interest

Please indicate how interesting you found the manuscript:

An article whose findings are important to those with closely related research interests

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

Needs some language corrections before being published

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Yes: Karla Hemming, University of Birmingham

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