PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of Xinjia Xuanbai Chengqi Decoction in Treating Acute Exacerbation of Chronic Obstructive Pulmonary Disease: Study Protocol for A Multicenter, Randomized, Controlled Trial
AUTHORS	Jin, Jin; Zhang, Hongchun; Li, Demin; Jing, Yue; Sun, Zengtao; Feng, Jihong; Zhang, Hong; Zhang, Yan; Cui, Tianhong; Lei, Xiang; Zhang, Jing; Cheng, Qijian; Li, Erran

VERSION 1 – REVIEW

REVIEWER	Yu-Chiang Hung Department of Chinese Medicine, Kaohsiung Chang Gung Memorial Hospital and School of Traditional Chinese Medicine, Chang Gung University College of Medicine, Taiwan.
REVIEW RETURNED	16-Apr-2019

GENERAL COMMENTS	Manuscript ID bmjopen-2019-030249 " Effectiveness of Xinjia Xuanbai Chengqi Decoction in Treating Acute Exacerbation of Chronic Obstructive Pulmonary Disease: Study Protocol for A Multicenter,Randomized, Controlled Trial" is reviewed. After reviewing this protocol, I have some comments for authors to improve the manuscript. 1. How many hospitals would be involved in this research? The authors said that is a multi-center trial be carried out in four comprehensive Third-grade first-class hospitals across China(page 3). However, authors details only showed three hospitals including China-Japan Friendship Hospital, Wangjing Hospital, and Affiliated Hospital of Tianjin University of TCM(Page 1). The other page 7 revealed the other three hospitals including Zhongshan Hospital, the First Affiliated Hospital,and Ruijin Hospital. 2. In general, acute exacerbation of chronic obstructive pulmonary disease treated with antibiotics would be at least 7 days. Why is the period about Xinjia Xuanbai Chengqi Decoction treating AECOPD for 5 days instead of 7 days? 3. What is the estimated power in this study? 4. The indication or criteria for Xinjia Xuanbai Chengqi Decoctio treating AECOPD would be the heat-phlegm and sthenic-fu syndrome.What are the definition, symptoms, and diagnostic criteria for the heat-phlegm and sthenic-fu syndrome ? I suggest that the author can discuss more content about he heat-phlegm and sthenic-fu syndrome of AECOPD . 5. What are the basic information or basic characteristics? Risk factors including smoking, age, and occupation should be collected and analyzed.

REVIEWER	Johannah Shergis RMIT University, Australia
REVIEW RETURNED	24-Apr-2019

GENERAL COMMENTS	I have some concerns about the study design and including the ability to repeat the study if required and generalizability of findings. 1.Please describe the herbal intervention and placebo in more detail to ensure you comply with the CONSORT extension for herbal interventions. Including Authentication method of each ingredient and how, when, where, and by whom it was conducted; statement of whether any voucher specimen was retained, and if so, where they were kept and whether they are accessible; Principles, rationale, and interpretation of forming the formula (why did you select this formula - need references). Quality control of each ingredient and of the product of the formula, if any. This would include any quantitative and/or qualitative testing method(s); when, where, how, and by whom these tests were conducted; whether the original data and samples were kept, and, if so, whether they are accessible; Safety assessment of the formula, including tests for heavy metals and toxic elements, pesticide residues, microbial limit, and acute/chronic toxicity, if any. If yes, it should be stated when, where, how, and by whom these tests were conducted; if the original data and samples were kept; and, if so, whether they are accessible. Your statement on Page 11: “The results of drug quality testing are consistent with the quality standards”, has no meaning. Also how did you come up with the dose of the formula? Did you convert the decoction to granule so does that mean all the herbs are cooked together and finally 5g is prepared for each participant per day? Also are the herbs for all participants made from the same batch? 2. sthenic-fu syndrome is not clearly defined and is not a term used in the WHO International Standard Terminologies on Traditional Medicine in the Western Pacific Region. I suggest you provide more description. Also, you did not describe how you will assess TCM syndrome of each participant. How will you ensure inter-rater reliability across hospitals? 3. Your primary outcomes are not validated outcomes for AECOPD. I suggest you consider treatment failure - Need to intensify therapy, relapse - treatment for AECOPD or hospital re-admission, lung function - early effect FEV1 (L or %), breathlessness - early effect Borg scale or VAS, duration of hospitalisation – Days, mortality after discharge (up to 3 months). Also, one month follow up is too short, maybe consider 3 months to align with other clinical trials in this area. 4. Consider frequent exacerbators in subgroup analysis. 5. How do you classify severity of AECOPD, you did not include a reference? Consider Celli 2007 Eur Resp J 29(6) 1224. 6. Sample size calculation – you should complete a proper sample size calculation based on the primary outcome that is used in another study eg. steroid or broncodilator. 7. Table 2 - you are using the Pharmaceutical name not Latin name. Eg. for Ku Xing Ren you should use the sciientific name, that is, Prunus armeniaca var. ansu. Also Semen Armeniacae Amarum should be Armeniacae Semen Amarum and Fructus Trichosanthis should be Trichosanthis Fructus. 8. You are proposing to use last observation carry-forward for

	imputation. However, you should consider worst case imputation because patients without data are likely that they deteriorated because they are inpatients

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1.I'm very sorry for the wrong cognition, because the study protocol was mainly designed and led by China-Japan Friendship Hospital, with assistance of Beijing Qihuang Medicine Clinical Research Center, National Center for Traditional Chinese Medicine, Wangjing Hospital of China Academy of Chinese Medical Sciences, Tianjin University of Traditional Chinese Medicine and Affiliated Hospital of Tianjin University of TCM, we wrongly thought the authors of protocol should be just composed of the above. Now the other three authors from Zhongshan Hospital, RuiJin Hospital and The First Hospital of China Medical University have been added.

2.First, in this study, we aim to compare the supplementation and replacement effect of xinjia xuanbai chengqi decoction on glucocorticoids, rather than antibiotics. Second, "REDUCE" study indicated that the effect of oral glucocorticoids on 5 d treatment is no less than that of 14 d glucocorticoid treatment, while the length of hospitalization is shortened(Leuppi JD, Schuetz P, Bingisser R,Et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary diseases: The REDUCE randomized clinical trial [J]. JAMA, 2013,309 (21) : 2223-2231. The DOI: 10.1001 / jama.2013.5023) .Finally, due to the financial constraints and management difficulties, we believe that shortening the course of treatment is beneficial to administration of this study.

3.Estimated power is 0.8.

4.Heat-phlegm and sthenic-fu syndrome is a typical syndrome type of traditional Chinese medicine based TCM characteristic theory "the Lung and the Large Intestine Are Interior-Exteriorl". Referred to “Retention of Heat-Phlegm in the Lung” syndrome in TCM Diagnosis and Treatment Guidelines for Chronic Obstructive Pulmonary Disease (2011), Heat-phlegm and sthenic-fu syndrome is defined as:

Primary symptoms: cough, wheezing, chest distress, yellow and white sticky sputum, abdominal distension, constipation, red tongue, yellow and greasy fur, slippery or rapid pulse;

Secondary symptoms: chest pain, facial blushing, thirst with desire to cold drinks, yellow urine, thick fur.

Diagnosis: (1) cough or shortness of breath;(2) yellow and white sticky sputum with difficult expectoration;(3) abdominal distension or constipation;(4) facial blushing;(5) thirst with desire to cold drinks;(6) yellow urine;(7) red tongue, yellow and greasy fur, slippery or rapid pulse.

The diagnosis should meet (1), (2) and (3), and two of (4), (5), (6) or (7).

5.I am very impressed by your observation. Study basic information including age, gender, height, weight, merge disease and treatment (malignant tumor, chronic congestive heart failure, diabetes, chronic renal insufficiency, hepatic insufficiency, disease of heart head blood-vessel, etc.) as well as the history and treatment of COPD, etc., which has included smoking history and history of occupational exposure, but we will in the future research separately to carry them out as an independent risk factor. Thank you very much!

Reviewer: 2

1.XJXBCQ Granules including Semen Armeniacae Amarum, Gypsum Fibrosum, Fructus Trichosanthis, Radix et rhizoma rhei, Scutellariae Radix, Perillae Fructus, Radix Glycyrrhizae Preparata, Rhizoma Fagopyri Dibotryis, Radix Asteris are produced and packaged by Anhui Jiren Pharmaceutical Co., Ltd. that have China Pharmaceutical Production License (Number: Wan 20160083). Authentication of above herbs is administrated absolutely according to Pharmacopoeia of the People's Republic of China 2015 by Anhui Jiren Pharmaceutical Co., Ltd. For example, Gypsum Fibrosum, heavy metals should not exceed 10mg/kg and arsenic salt should conform to specifications on the basis of Pharmacopoeia of the People's Republic of China 2015. China Certificate of Good

Manufacturing Practices for Pharmaceutical Products, China Pharmaceutical Production License of Anhui Jiren Pharmaceutical Co., Ltd. and herbal testing reports will be uploaded as supplements. Xinjia Xuanbai Chengqi Decoction is changed addition or subtraction from Xuanbai Chengqi Decoction, TCM classical prescription from Item Differentiation of Warm Febrile Diseases. We come up with the dose of the formula according to clinical experience. All herbs will be decocted together complying with processing technology and finally be made into granule. Participants take 5g at a time, three times a day for 5 days. Herbs for all participants made from the same batch.

2.Heat-phlegm and sthenic-fu syndrome is a typical syndrome type of traditional Chinese medicine based TCM characteristic theory "the Lung and the Large Intestine Are Interior-Exteriorl". Referred to “Retention of Heat-Phlegm in the Lung” syndrome in TCM Diagnosis and Treatment Guidelines for Chronic Obstructive Pulmonary Disease (2011) , Heat-phlegm and sthenic-fu syndrome is defined as:

Primary symptoms: cough, wheezing, chest distress, yellow and white sticky sputum, abdominal distension, constipation, red tongue, yellow and greasy fur, slippery or rapid pulse;

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The diagnosis should meet (1), (2) and (3), and two of (4), (5), (6) or (7).

In the initial stage of the protocol formulation, we held several demonstration meetings to ensure that the researchers in each center clearly defined the Inclusion and exclusion criteria of this study. Then the researcher's manual also has been printed. After initiation of the study, we will assign special person to each center to instruct the enrollment of the first patient. In addition, Beijing Qihuang Medicine Clinical Research Center is qualified for Contract Research Organization(CRO). They will provide regular telephone visits (1 time per week) and on-site visits (1 time per month in peak period and 1 time per 2 months in moderate period) to ensure inter-rater reliability across hospitals.

3.The diagnosis of AECOPD is mainly based on clinical symptoms such as shortness of breath, accompanied by wheezing, chest distress, aggravated cough, increased sputum volume, changes in sputum color and/or viscosity, and fever(Expert group on diagnosis and treatment of AECOPD. Chinese Expert Consensus on diagnosis and treatment of Accelerated Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)(Updated 2017). International Journal of Respiration.2017;37(14): 1041-1057). Therefore, the treatment goal of AECOPD is to reduce the severity of acute exacerbations and prevent the recurrence of acute exacerbations. Pulmonary function tests are not recommended for patients with acute exacerbations because them often have difficulty in performing pulmonary function tests satisfactorily(GOLD Executive Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease(Revised 2013).www.goldcopd.com). AECOPD patients cannot cooperate and the results are not accurate. So we chose some current indicators as primary outcomes. 30 days Follow-up is recommended in the 2017 GOLD guidelines(Global Initiative for Chronic Obstructive Lung Disease(GOLD):Global Strategy for the Diagnosis, Management and prevention of Chronic Obstructive Pulmonary Disease.(2017 REPORT).http://www.goldcopd.org). We will consider a 3 months or more follow-up for future if if condition allowed.

4.Yes, we will find those with frequent exacerbations during follow-up, and then conduct subgroup analysis and comparison in research results report finally.

5.Sorry, it was our fault that not making it clear. References have been added in the protocol. Thank you very much!

6.According to our pre-experiment, comparing symptom scores of patients before and after treatment, the average score was 10.67±2.61 on admission, 4.33±1.97 on the 6th day of admission, and the difference value was 6.33±3.73. Excellent efficiency test will be conducted between Integrated Chinese and Western Medicine Group A and Western Standard Medicine Group C, meanwhile non-inferiority test will be conducted between Integrated Chinese and Western Medicine Group B and Western Standard Medicine Group C. Cut-off point is defined as 1, so expected difference of excellent

efficiency test should be more than 7.33(6.33+1), and which of non-inferiority test should be not less than 5.33(6.33-1). When the power=0.8, each of the three groups required 100 effective cases. Considering a 20% shedding rate, a total of 360 cases were needed in the three groups, with 120 cases in each group.

7.Respected professor：According to Pharmacopoeia of the People's Republic of China 2015, nomenclature of Latin name of herb is specie ahead and medicinal position later. All Latin names of herbs in Table 2 are modified to be consistent with Pharmacopoeia of the People's Republic of China 2015. Please check Supplements.

8.Yes, you are right. Patients are likely to deteriorate even exit due to poorly controlled, but all these have been initially considered in the design. First, we have designed a 20% loss rate. Second, since participants are hospitalized patients, once deterioration occurred investigator will start emergency unblinding to insure the rescue program, recorded as adverse events. These are all in ethical preparations.

VERSION 2 – REVIEW

REVIEWER	Johannah Shergis RMIT University, Australia
REVIEW RETURNED	05-Aug-2019

GENERAL COMMENTS	1. Manuscript needs careful proof reading. There are a few spelling and grammatical errors. 2. Introduction - reference 6. The statement you make in the text is not supported by this reference. Consider a different reference or re phrase the sentence. 3. Need to provide more information about the classification of exacerbations. 4. GOLD guidelines recommend 40mg of prednisone. You care giving Budesonide. Is this the GOLD standard steroid treatment for AECOPD? 5. Did all participants have confirmed bacterial infection? Or suspected bac. Infection? Increased sputum purulence, dyspnea and volume? Chest x-ray? Did you rule out pneumonia? 6. Major issue: Recommend to follow up at 3 months to ensure they have returned to a stable clinical state. 7. “The results of drug quality testing are consistent with the quality standards”. What quality standards. Do you mean GMP? “All herbs were tested to the same standard.” What do you mean same standard? 8. What is the TCM syndrome score? You need to give more details. What syndromes were included? Did you conduct CM syndrome diagnosis? 9. Major issue: Need more details about the herbs. Need to meet the CONSORT statement for herbal interventions. 10. Why did you choose this herbal formula? 11. How was the sample size calculated?

VERSION 2 – AUTHOR RESPONSE

1.Sorry sir, because English is not the first language, writing is not very skillful. We have tried our best to check it.

2.Thank you for suggestion. The expression was not proper and has been corrected.

3.Referring to GOLD guidelines, Celli 2007 Eur Resp J 29(6) 1224, etc., we have fully considered the COPD exacerbation, including heart failure, cardiac arrhythmia, hypertension, diabetes, and progressing to AECOPD level III to ICU admission even mechanical ventilation. Patients who can't tolerate LVFX or whose condition have not been alleviated but even aggravated after 3 days of treatment, we will adjust the antibacterial therapy according to the regulations in the Chinese Expert Consensus for the Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) (Updated 2017). The reasons for adjustment of the antibacterial drug program will be recorded in detail. All above have been fully taken into account, and described specifically in the manuscript on page 13.

4.Sure, GOLD guidelines recommend 40mg of prednisone. However, due to this trail is a placebo control study, when we contacted the pharmaceutical manufacturers for making placebo but found that they were unable to produce 40mg tablets, which was vital to double-blind. There are also problems in the production of intravenous injection agents. In the initial stage of the protocol formulation, clinical experts indicated that it was unfrequent to take systemic venous glucocorticoid for 5 days for patients of AECOPD clinical grade I-II. After referring to relevant literatures, we found that atomized Budesonide is also recommended as a substitute for oral hormones in the treatment of patients with acute exacerbations of COPD. Most of all, using Budesonide atomized inhalation is fully convenient to implement placebo control. So we chose Budesonide atomized inhalation finally.

5.Yes, all enrolled patients will be assessed by clinicians at the screening stage. Participants must meet indications of antimicrobial therapy for AECOPD, i.e., dyspnea, increased sputum volume, and purulent sputum, or just two of the three symptoms but including purulent sputum. Chest CT or X-ray is a necessary item during the screening period, which is used to exclude interfering diseases such as pneumonia, bronchiectasis, tuberculosis, pulmonary fibrosis or lung cancer.

6.Professor, thank you for your advice. In combination with the GOLD guidelines, follow-up at 1 month after discharge is conducted to evaluate the effect of hospitalization and re-admission rate within 30 days after discharge, and follow-up at 3 months is conducted to confirm whether the patient have returned to a stable clinical state. Your advice is acceptable but the first participant has been enrolled at 7 Jan 2019. In the early stage, we also found some followed-up for 1 month in other research reports（ie, Tashkin DP, Celli B, Senn S, etc. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008 Oct 9;359(15):1543-54.）. It has been indicated in limitations of this study that a 1-month follow-up period may be a bit short. We will conduct a 3 months or more follow-up for future if condition allowed. Thanks very much!

7.Dear professor, as I replied last time, the quality testing standard for all herbs is Pharmacopoeia of the People's Republic of China 2015, the latest and most authoritative pharmacopoeia in China. We purchase experimental drugs from pharmaceutical companies that are qualified to comply with the standards of Pharmacopoeia of the People's Republic of China 2015. For example, the Chinese pharmacopoeia requires that the peroxidation value of Armeniacae Semen Amarum should not exceed 0.11, the value of herb we purchased is 0.05. The residual sulfur dioxide should not exceed 150mg/kg, and our detection value is 45mg/kg. Amygdalin (C20H27NO11) should be at least 3.0% and our detection value is 4.9%. All are in compliance with quality standards of Pharmacopoeia of the People's Republic of China 2015. As for Gypsum Fibrosum, the Chinese pharmacopoeia requires heavy metals not to exceed 10mg/kg, and the quality report shows "compliance". All herbs comply

with the standards of Pharmacopoeia of the People's Republic of China 2015. Please see the attachments for the quality inspection reports.

8.I am sorry that I did not describe the evaluation criteria of TCM syndrome score in detail due to length limitation. The scoring scale has now been added.

9.Professor, after getting your advice, I referred to the relevant literatures and found that Joel Gagnier et al. revised and expanded the Reporting Randomized, Controlled Trials of Herbal Interventions: An Elaborated CONSORT Statement based on the 22 CONSORT items. It is particularly noteworthy that this trail is to study granules from a classic recipe under the guidance of TCM theory. In addition to the effective ingredients of various herbs, it also has the characteristics of TCM prescription theory, such as the compatibility of principals, associates, adjuvants and messengers, mutual promotion, mutual enhancement and so on, rather than a study on the ingredients of single herb. CONSORT statement is not suitable for TCM with characteristics such as syndrome differentiation and treatment and cannot reflect the clinical characteristics of TCM. For example, not all herbal interventions have the proprietary product name (ie, brand name) or the extract name (eg, EGb-761) and the name of the manufacturer of the product (item 4a2), and they may simply be tailored by investigator for the study. Similarly, since we're not studying single herb, “Product’s chemical fingerprint and methods used (equipment and chemical reference standards) and who performed it (eg, the name of the laboratory used). Whether or not a sample of the product (ie, retention sample) was retained and, if so, where it is kept or deposited (item 4D.1)” is not suitable too. Therefore, the CONSORT statement will be more applicable to the study of single herb or herbal extracts than the study of TCM formulations. As TCM study is still in the process of being improved and global, we can just guarantee that the herbal sources used in this trail are qualified, legal, completely safe and reliable in China.

10.Xinjia Xuanbai Chengqi Decoction is changed addition or subtraction from Xuanbai Chengqi Decoction, which is a classic prescription of TCM from Item Differentiation of Warm Febrile Diseases for Heat-phlegm and sthenic-fu syndrome. Modern clinical physicians represented by Enxiang Chao, the TCM Master, have rich clinical experience in treating Heat-phlegm and sthenic-fu syndrome of acute exacerbation of COPD. The clinical feedback also proves that this method can effectively improve clinical symptoms and get patients out of danger quickly. Therefore, we made a small amount of addition and subtraction according to the actual experience on the basis of this prescription, and named it Xinjia Xuanbai Chengqi Decoction for further clinical research.

11.According to our pre-experiment, comparing symptom scores of patients before and after treatment, the average score was 10.67±2.61 on admission, 4.33±1.97 on the 6th day of admission, and the difference value was 6.33±3.73. Excellent efficiency test will be conducted between Integrated Chinese and Western Medicine Group A and Western Standard Medicine Group C, meanwhile non-inferiority test will be conducted between Integrated Chinese and Western Medicine Group B and Western Standard Medicine Group C. Cut-off point is defined as 1, so expected difference of excellent efficiency test should be more than 7.33(6.33+1), and which of non-inferiority test should be not less than 5.33(6.33-1). When the power=0.8, each of the three groups required 100 effective cases. Considering a 20% shedding rate, a total of 360 cases were needed in the three groups, with 120 cases in each group.

VERSION 3 – REVIEW

REVIEWER	Johannah Shergis RMIT University Australia
REVIEW RETURNED	19-Sep-2019

GENERAL COMMENTS	Thank you for addressing the comments