PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Study design for a randomized controlled trial to explore the modality and mechanism of Tai Chi in the pulmonary rehabilitation of chronic obstructive pulmonary disease
AUTHORS	Fu, Juan-juan; Min, Jie; Yu, Peng-ming; McDonald, Vanessa; Mao, Bing

VERSION 1 - REVIEW

REVIEWER	Pan Lei Department of Respiratory and Critical Care Medicine, Binzhou Medical University Hospital, China
REVIEW RETURNED	16-Feb-2016

GENERAL COMMENTS	Comments to the Author With great interest I have read the paper of Fu et al. In general, Fu and colleagues presented a well-designed study protocol to explore the modality and mechanism of Tai Chi in the pulmonary rehabilitation of chronic obstructive pulmonary disease. However, some issues still need to be addressed. Major comments: - Participants A detailed description of the patient inclusion and exclusion criteria is required. Please describe some of the details. - Randomization and blinding Please describe some of the details on blinding. Why not to use double-blind? - Sample size The authors should focus on study withdrawal. Participants will be informed that they can withdraw from the study at any given point and that this will not affect their future care. During the 12-month follow up, participants may be withdrawn from the trial either at their own request or at the discretion of the investigator. The authors should pay attention to these effects on the sample size, and describe the content. - Please describe the recruitment process. In fact, patient recruitment is very difficult, especially in China. - Intervention Please describe the details of intervention about Tai Chi, TBRS, and usual care, respectively. - Outcome measurement The overall treatment effect should be compared with its minimum clinically important difference (MCID), which is defined as the smallest change in the measurement used to evaluate the clinical significance of intervention effects. The relationship of the anchor-based MCID to distribution-based smallest (statistically) significant

	differences has been illustrated in several studies (J Clin Epidemiol 2008;61:102–9; J Clin Epidemiol 2010;63:37–45). - Inflammatory mediators and immune function Why the authors chose these indicators, based on the presence or absence? Please indicate reference(s). - Statistical analysis An intention-to-treat (ITT) analysis should be applied. The authors should pay attention to study withdrawal. Participants may be withdrawn from the trial either at their own request or at the discretion of the investigator. If so, the data collected to date cannot be erased and may still be used in the final analysis. - DISCUSSION There is lack of refinement in the Discussion section. This manuscript is just a study protocol, which should focus on step programs of research program, especially on innovation and limitations. In short, the Discussion section should to be re-organized and refined to make it more logical and readable.

REVIEWER	Yan Yang Jining hospitial, China
REVIEW RETURNED	18-Feb-2016

GENERAL COMMENTS	The RCT was designed to assessed the effects of Tai Chi for COPD. Some minor comments are as follows: 1. Page 6, Line 14-19 are redundant. 2. How to choose dose of Tai Chi exercise? 3. Authors should use an editorial assistant to improve the readability of this manuscript.

REVIEWER	Dr Louise Wiles - Patient Safety and Healthcare Human Factors Group - Centre for Population Health Research (CPHR) - University of South Australia (UniSA) AUSTRALIA
REVIEW RETURNED	23-Mar-2016

GENERAL COMMENTS	GENERAL COMMENTS 1. I would like to strongly recommend that the authors seek review of their manuscript from a professional editor. There are exceptionally high numbers of spelling and grammatical errors throughout the document. 2. I found some sweeping statements were made within the body of text that were either inaccurate or incorrect (with no justification or rationale provided to support the claims). An example to illustrate both points above is: Abstract - "...the strength and weakness of Tai Chi compared to conventional PR, which is a superior modality of Tai Chi exercise..." Please provide justification for anticipating a 20% drop-out rate (i.e. cite supporting research articles) STRENGTH OF THE STUDY 3. Suggest limit the dot points to the main study strengths rather than including additional superfluous study characteristics. As an

	example, the first three dot-points could be combined to read as: "...Compare and contrast the feasibility and outcomes following three PR interventions using a robust RCT methodology..." 4. I feel the main strength in relation to dot-point 4 is the length of follow-up, so this information should be added here. LIMITATIONS OF THE STUDY 5. One of the major limitations of this study will be the applicability to other populations, healthcare settings and cultural contexts where Tai Chi may not be as well established as it is in China. INTRODUCTION 6. I didn't feel that the authors provided sufficient rationale for incorporating and testing Tai Chi within the RCT intervention arm(s). Both Tai Chi and standard PR programs can be adapted to ensure flexibility with time and venue, cost-effective, and community or home-based; I would encourage the authors to scope the breadth/depth of literature around this (especially for standard PR programs). I think a stronger argument could be the characteristics of Tai Chi which are not necessarily part of standard PR programs (i.e. mindfulness and incorporating functional movements with breathing control); this could be particularly beneficial for people with COPD where chronic sensations of dyspnoea are commonly an issue. METHODS - DESIGN 7. The screening visit and run-in period is designed to provide participants with "education and training of both Tai Chi and TBRS exercise to exclude those who cannot tolerate the exercises and enhance study compliance". If you proceed with this approach, there are two major considerations here: (a) pre-selecting participants in this way will substantially skew your results towards populations who are 'healthier' and/or have a greater level of fitness - this will be a major limitation for your study (and should be documented as such) (b) in clinical practice, PR programs are designed to be adaptable and accommodating of people regardless of their levels of physical fitness - again, this will be a major limitation to the applicability of your results/findings to clinical practice METHODS - SAMPLE SIZE 8. Based on the authors' calculations, in order to undertake four-group comparisons (and factoring in 20% drop-out) I would suggest that a larger sample size should be the aim (i.e. n>30, power 0.83) if it is within the project scope. METHODS - MONITORING OF EXERCISE INTENSITY 9. Suggest that Borg PRE (which is a common PR measure of exercise intensity) should be included for use here as well. Participants who are prescribed beta-blockers may have a blunted cardiovascular response to exercise. METHODS - COPD RELATED EDUCATION 10. It is not clear whether all groups will receive education (i.e. protocol states only the control group will receive weekly education). Suggest this needs to be standardised across all groups. METHODS - OVERALL 11. What processes and procedures will be used to ensure

	Research Assistants (RAs)/Researchers are adequately qualified/trained to undertake outcome measurement/assessments? (i.e. certified Tai Chi instructor versus RAs for TBRS exercise who may/may not be experienced in PR). 12. How will you control for participants prior exposure/participation in PR programs and/or Tai Chi exercise? i.e. eligibility criteria for inclusion 13. Which staff will undertake PFTs? The detail regarding personnel involved, their level of training/certifications etc. need to be included. 14. It is a bold aim to "explore the potential mechanisms of Tai Chi in COPD by addressing the level of systemic inflammation". Suggest the use of tempered (i.e. more passive) language here as there may be many other mechanisms by which Tai Chi and PR produce outcomes (i.e. other hormonal profiles, genetic factors etc.). STATISTICAL ANALYSIS 15. Suggest that the authors need to consider detailing if/which multiplicity correction factor(s) will be applied.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

With great interest I have read the paper of Fu et al. In general, Fu and colleagues presented a well-designed study protocol to explore the modality and mechanism of Tai Chi in the pulmonary rehabilitation of chronic obstructive pulmonary disease. However, some issues still need to be addressed.

Major comments:

1. Participants

A detailed description of the patient inclusion and exclusion criteria is required. Please describe some of the details.

Author response: We have detailed the inclusion and exclusion criteria in the manuscript on Page 7-8 as following: “Participants will be included if they (1) are diagnosed with COPD; (2) have a moderate to severe severity of COPD as defined by 30%≤ post-bronchodilator forced expiratory volume in 1 second (FEV1) <80% predicted; (3) are between 45 to 75 years; (4) are clinically stable confirmed by the absence of using systemic corticosteroids and/or antibiotics, emergency room visits or hospitalisations in the past 4 weeks;1 and (5) are willing to give written informed consent. The exclusion criteria included the following: (1) GOLD stage 4 defined by post bronchodilator FEV1 <30% predicted; (2) coexistence of other chronic respiratory disorders; (3) presence of severe comorbidities such as haematologic or solid organ malignancy, symptomatic CVD, musculoskeletal or neurological disease that might affect ambulation or exercise training; (4) cognitive dysfunction, metal disorder or abnormal behaviours; (5) participation in a PR programme in the past 12 months; and (6) currently practicing Tai Chi or participation in a clinical trials of COPD and other diseases.”

2. Randomization and blinding

Please describe some of the details on blinding. Why not to use double-blind?

Author response: Participants will receive inform consent which include the type of exercise of the study. Due to the nature of the exercise modality of Tai Chi and conventional PR using total body recumbent stepper (TBRS), the difference between intervention groups are obvious to the study participants, therefore it is not possible to blind either participants or research physiotherapist and Tai Chi instructors for the types of exercise.

In terms of blinding, we have revised in the manuscript on Page 8 as following: “The allocation sequence will be kept in sequentially numbered, opaque and sealed envelopes. The main investigator

and data analyst will not be involved in any interventions and will be blinded to group allocation. Outcome assessors evaluating the effects of the treatments will also be blinded to the allocation of treatments. Participants, research physiotherapists and Tai Chi instructors that supervise the exercise will not be blinded to the allocation. Once allocation takes place, the research physiotherapist and Tai Chi instructors will receive a copy of the participant number and allocation, and the outcome assessor will be informed of the participant number only. To maintain observer blindness throughout the study period, participants will be requested not to discuss the intervention with the outcome assessors."

3. Sample size

The authors should focus on study withdrawal. Participants will be informed that they can withdraw from the study at any given point and that this will not affect their future care. During the 12-month follow up, participants may be withdrawn from the trial either at their own request or at the discretion of the investigator. The authors should pay attention to these effects on the sample size, and describe the content.

Author response: We agree with the reviewer that the withdrawal or drop-out of the participants in RCTs would affect the sample size resulting in insufficient power to detect a real effect. In order to maintain participant retention and the completion of follow-up, we have developed several strategies and added in the manuscript on Page 15-16 as following: "Strategies to optimize participant retention and complete follow-up are developed including (1) involve well-trained research personnel and provide training to study staff with tips for educating and motivating the participants; (2) provide study-specific education to the participants; (3) involve the family or caregivers of the participants; (4) schedule appointments in advance and send reminders; (5) offer after work hours or weekend visits; (6) allow rest between tests as needed. If the participant fails attend the follow-up visit, a completion of questionnaires via telephone or email is allowed to achieve as much as the measures."

In addition, as suggested by several reviewers, we enlarge the sample size to increase the power of the study and ensure sufficient number of participants would complete the study. The calculation is as following: The number of participants needs to be recruited for each group is the calculated sample size plus a 20% drop-out. A drop-out rate of 10% is usually estimated in previous studies, and a drop-out rate >20% poses serious threats to validity of the study.2,3 In this case, the loss can cause significant bias with mistrusting results and lead to failed RCT.2. In case there is a greater drop-out rate related to the long-term follow-up, we estimate a drop-out rate of 20% to increase the sample size and ensure that the achievement of the calculated sample size. Based on our calculation, the recruitment of 25 to 30 participants would achieve a statistical power range from 0.74 to 0.83. As suggested by reviewer 3, to achieve a statistical power >0.8 the number of the participants that complete study should be ≥30 per group. Factoring in the 20% drop-out, the sample size should aim at 38 for each groups. [formula=30/(1-0.2), n=37.5]. Therefore, we have increased the sample size and revised it in the manuscript on Page 9 as following:

"The sample size calculation of this study is based on the St. George Respiratory Questionnaire (SGRQ) total score in the study by Chan et al.4 By computing the changes in the SGRQ total score in the Tai Chi group and in the self-practice group (breathing and self-pacing walking exercise) before and after the interventions, 25 participants per group would be required to achieve a power of 0.8 and a significance level of 5% for difference detection. Furthermore, we conducted a power analysis using the fpower function in STATA 13.0 (Stata Corp., Tex., USA) to estimate the sample size needed to perform four-group comparisons provided that an alpha is set as 0.05. The results showed that a recruitment of 25 participants would achieve a statistical power of 0.74, and 30 participants would achieve a power of 0.83. A sample size of 38 participants per group, inclusive of a 20% dropout compensation,2,3 will be applied for this trial. Therefore, 38 participants per group and a total of 152 participants is a reasonable sample size for this study."

The revision of study protocol related to the sample size has been approved the Institutional Review Board (IRB) and updated in the Chinese Clinical Trial Registry (ChiCTR-IOR-15006874).

4. Please describe the recruitment process. In fact, patient recruitment is very difficult, especially in

China.
Author response: We agree with the reviewer that the participant recruitment is difficult to some extent in China. We are holding a GLP centre for traditional Chinese medicine in the hospital and in west China, and there are several large clinical databases available for the recruitment of various clinical trials. In addition, we have been granted to set a clinical database and biobank specifically for COPD by local medical council, and several clinical studies and clinical trials has been completed based on this database.
In terms of the details of participant recruitment, we have added in the manuscript on Page 7 as following: “Patients with COPD in our clinical database will be invited, and other recruitment resources include advertisements in West China Hospital, Chengdu, China and community hospitals. Potential participants will be contacted over the phone to assess their basic eligibility for the study. Individuals interested in the study that also meet the basic eligibility criteria will be scheduled for a screening visit and the informed consent process.”

5. Intervention
Please describe the details of intervention about Tai Chi, TBRS, and usual care, respectively.
Author response: We have added the detailed description of the interventions about Tai Chi, TBRS and usual care in the “Intervention” section on Page 9-11 and “COPD-related education” on Page 12. Moreover, we have also revised the contents under “Monitoring of exercise intensity” on Page 11-12 to further elaborate the exercise protocols.
“Yang-style Tai Chi, in its many variations, is the most popular and widely practiced style in the world; therefore, participants allocated to the Tai Chi group of this study will undergo the simplified 24 forms Yang-style Tai Chi training at the rehabilitation centre of the hospital. The 24 forms Yang-style Tai Chi consists of 24 standard movements as described in Table 3 and Figure 2a. The certified Tai Chi instructor will explain and demonstrate the Tai Chi principles and the practicing techniques and safety precautions of each movement at the beginning of the study, and the instructor will review these principles and techniques as needed throughout the course of the study. An instructor will always practice with the participant to demonstrate and correct the Tai Chi movements. Participants are also instructed to focus and perform traditional Tai Chi breathing, such as along breathing, against breathing, dan tian breathing (deep abdominal breathing) and whole body breathing methods, together with the body movements.
The conventional rehabilitation exercise in this study uses TBRS (Humaneotec Co., Ltd, Guangzhou, China) (Figure 2b). A research physiotherapist will educate the participant about the equipment, exercise protocol, termination criteria and emergency notice before starting the exercise. Once the participant is seated in the TBRS, necessary adjustments are made for leg and arm length according to the methods used by Billinger et al.5 The participant will be instructed to place the arms and feet in the desired position, pushing or pulling the upper arm grips and pedalling simultaneously. The exercise protocol will start at a stepping cadence of 40 to 60 steps×min-1.
In the combined exercise group, the participant will start with TBRS exercise lasting for 15 minutes, followed by 15 minutes of Tai Chi exercise.
Participants in all study groups will continue with their usual medical care during the full study period. Participants in the control group will not perform PR but can maintain their home-based exercise on the consideration that a small number of patients with COPD in China have access to PR.
Monitoring of exercise intensity
To design a controlled trial with comparable exercise intensity in different exercise groups, the participants’ HR and oxygen saturation will be monitored while they practice a full set of exercises. Previous reports6,7 have demonstrated that Tai Chi is an exercise with moderate intensity. The COPD rehabilitation guideline8 recommends moderate intensity to ensure effective exercise. The research physiotherapists or Tai Chi instructors will supervise and prompt participants to achieve moderate exercise intensity. In the Tai Chi group, participants will also be asked to imagine pushing against resistance during movements, to squat lower, or to take larger steps in certain movements to increase the intensity of exercise. Participants in the TBRS group will be instructed to speed up and/or

increase resistance to achieve the exercise intensity. For a moderate exercise intensity, a target HR between 40% to 59% of the heart rate reserve (HRR) is required according to American College of Sports Medicine criteria.9 For individuals taking beta-blocker medications, the rate of perceived exertion using the Borg 6-20 scale will be applied to achieve target exercise intensity, and a score of 12 to 14 is categorised as moderate-intensity exercise.10 The formula to calculate a target HR is given as follows:9

Target HR= ((220-age)-resting HR) × aiming % + resting HR

COPD related education

Participants in all four groups will receive the same weekly educational sessions. The contents include smoking cessation, diagnosis, COPD medications, action plan, exacerbations, nutrition, and self-management, such as infection prevention, inhalation technique, breathing and coughing techniques.

- Outcome measurement

The overall treatment effect should be compared with its minimum clinically important difference (MCID), which is defined as the smallest change in the measurement used to evaluate the clinical significance of intervention effects. The relationship of the anchor-based MCID to distribution-based smallest (statistically) significant differences has been illustrated in several studies (J Clin Epidemiol 2008;61:102–9; J Clin Epidemiol 2010;63:37–45).

Author response: We agree with the reviewer that the treatment effect of a clinical trial should be compared with the MCID of the selected outcomes. The primary outcome of the current study is SGRQ, and the second outcomes include 6MWD, CAT score and pulmonary function et al. For COPD study, the MCIDs for these outcomes have been established11-14 and widely used in previous studies, we will compare the treatment effect of different exercise modalities to these MCIDs in the data analysis. Therefore, we have added this in the “Statistical analysis” on Page 16-17 in the manuscript as following: “The treatment effect of different exercise modalities on continuous outcomes will be measured by the difference in the means and compared to the minimal clinically important differences (MCIDs) to determine the clinical importance.15”

- Inflammatory mediators and immune function

Why the authors chose these indicators, based on the presence or absence? Please indicate reference(s).

Author response: Systemic inflammation is of great importance in the pathogenesis of COPD, which is also related to clinical outcomes of COPD. Study on the possible mechanism of the therapeutic effect of Tai Chi on COPD is absent. Based on the effect of Tai Chi on inflammation reduction and immune regulation shown in previous studies16-18, we hypothesize that the possible therapeutic effect of Tai Chi on COPD may be associated with a reduction in systemic inflammation. The reason why we chose these biomarkers is because they are classic inflammatory mediators represent the level of systemic inflammation and immune function in various diseases and also in COPD. Additionally, some of these markers have been shown to be involved in the treatment effect of Tai Chi. However, whether Tai Chi impact the levels of these systemic inflammatory markers in COPD contributing to the clinical benefits of Tai Chi remains unclear. Therefore, we chose these well-recognized mediators represent systemic inflammation to test the hypothesis. The reason and references related have been complemented in the manuscript on Page 21-22 as following: “Increasing evidence indicates that COPD is a complex disease characterised by airflow obstruction and airway inflammation. Systemic consequences and a variety of comorbidities are also involved. These systemic consequences and comorbidities include exercise intolerance, skeletal muscle dysfunction, metabolic dysfunction, osteoporosis, CVD and excessive mortality.19 The mechanisms of these systemic manifestations are unclear, although systemic inflammation is hypothesised to be of predominant importance. Systemic inflammation is defined as an elevation of pro-inflammatory cytokines or acute-phase reactants in the circulation.20 C-reactive protein and IL-6 are classic mediators representing the level of systemic inflammation in various diseases including COPD,21,22

and our previous studies demonstrated the presence and their important role in COPD.23 TNF-α and IL-8 are also crucial pro-inflammatory cytokines involved in the systemic inflammatory response in COPD.21,24,25 A variety of mind-body exercises, including Tai Chi, have been shown to be associated decreased inflammatory markers such as CRP16, monocyte induced inflammation and immune regulation18 in different clinical populations.17 However, the effect of Tai Chi on the levels of circulating inflammatory mediators in patients with COPD remains unclear. Given the benefits of Tai Chi on COPD and on other diseases, e.g., osteoporosis and CVD, which are the most commonly observed comorbidities of COPD, it is possible that the suppression of systemic inflammation might be one of the mechanisms underlying the treatment effects of Tai Chi in COPD. Therefore, we will test the above hypothesis by examining the levels of these biomarkers before and after treatment inventions during the study."

- Statistical analysis
An intention-to-treat (ITT) analysis should be applied. The authors should pay attention to study withdrawal. Participants may be withdrawn from the trial either at their own request or at the discretion of the investigator. If so, the data collected to date cannot be erased and may still be used in the final analysis.
Author response: We agree with the reviewer that an intention-to-treat (ITT) analysis should be applied especially for our study that has multiple training visits and long-term follow up. We have added this in the manuscript on Page 16 as following: "Intention-to-treat analysis will be applied to include all randomized participants, and the missing data will be analyzed according to the last-observation-carried-forward rule."

- DISCUSSION
There is lack of refinement in the Discussion section. This manuscript is just a study protocol, which should focus on step programs of research program, especially on innovation and limitations. In short, the Discussion section should to be re-organized and refined to make it more logical and readable.
Author response: We have carefully revised and refined the discussion to focus on the rationales, the innovations and limitation of the current study, as shown on Page 18-23 in the manuscript.

Reviewer 2:
The RCT was designed to assessed the effects of Tai Chi for COPD. Some minor comments are as follows:
1. Page 6, Line 14-19 are redundant.
Author response: We have reviewed the PDF document in the first submission and found the contents in Line 14-19 on Page 6 are not continuous. We have contacted with the editor trying to find out what this comment means. The editor replied that they will try and find out from the reviewer, however we haven't received the reply before the submission of a revised manuscript. We thought the contents that the reviewer refers to in the PDF document are: "in which modality Tai Chi is practiced that can benefit patients with COPD maximally, compensating the limitation of conventional PR and better solving current clinical problems are still unknown." "In terms of the mechanisms of the therapeutic effects of Tai Chi, an increasing number of studies have revealed that Tai Chi can impact inflammatory process and immune response in clinical populations and healthy controls."
If the reviewer means the above contents, we think that these statements raise the research questions and describe the mechanisms of therapeutic effect of Tai Chi concluded from previous studies, which should be maintained in the manuscript. We have made some revisions about these words to make the statements more accurate as following: "Therefore, although either Tai Chi26-31 or conventional PR32 alone has been demonstrated to be beneficial to COPD, there are still many unknowns to better solve current clinical problems, such as how Tai Chi compares to conventional PR in terms of its pros and cons in COPD, if it is possible for Tai Chi to replace conventional PR, which modality of Tai Chi provides the maximal benefit to COPD patients, and how to compensate the limitation of conventional PR. In terms of the mechanisms of the therapeutic effects of Tai Chi, an

increasing number of studies have revealed that Tai Chi can affect inflammatory processes and immune responses in clinical populations and healthy controls."
If the reviewer did not refer to the above contents, we would like to revise and answer this question again after the clarification of this comment.

2. How to choose dose of Tai Chi exercise?
Author response: We have reviewed all the randomized controlled trials as listed in Table 1. The frequency of Tai Chi training ranged from 2 to 3 times per week, and each class lasted from 15 to 60 minutes. The total training period ranged from 8 weeks to 6 months. In addition, ATS/ERS statement of PR33 recommends 3 times per week and a minimum of 20 sessions of supervised exercise sessions should be given, and the effective training time should reach to 30 minutes for each session. Based on the previous studies and recommendations, 30-minute Tai Chi rehabilitation programme 3 times per week for a total of 8 weeks (24 sessions) will be applied in this study.
In terms of the exercise intensity, we have complemented the statement in the manuscript on Page 11 as following: "To design a controlled trial with comparable exercise intensity in different exercise groups, the participants' HR and oxygen saturation will be monitored while they practice a full set of exercises. Previous reports6,7 have demonstrated that Tai Chi is an exercise with moderate intensity. The COPD rehabilitation guideline8 recommends moderate intensity to ensure effective exercise. The research physiotherapists and Tai Chi instructors will supervise and prompt participants to achieve moderate exercise intensity. In the Tai Chi group, participants will also be asked to imagine pushing against resistance during movements, to squat lower, or to take larger steps in certain movements to increase the intensity of exercise. Participants in the TBRS group will be instructed to speed up and/or increase resistance to achieve the exercise intensity. For a moderate exercise intensity, a target HR between 40% to 59% of the heart rate reserve (HRR) is required according to American College of Sports Medicine criteria.9 For individuals taking beta-blocker medications, the rate of perceived exertion using the Borg 6-20 scale will be applied to achieve target exercise intensity, and a score of 12 to 14 is categorised as moderate-intensity exercise.10 The formula to calculate a target HR is given as follows:9
Target HR= ((220-age)-resting HR) × aiming % + resting HR"

3. Authors should use an editorial assistant to improve the readability of this manuscript.
Author response: We have sent the manuscript to AMJ English-language editing service to improve the readability.

Reviewer: 3
GENERAL COMMENTS
1. I would like to strongly recommend that the authors seek review of their manuscript from a professional editor. There are exceptionally high numbers of spelling and grammatical errors throughout the document.
Author response: We have sent the manuscript to AMJ English-language editing service to improve the readability.

2. I found some sweeping statements were made within the body of text that were either inaccurate or incorrect (with no justification or rationale provided to support the claims).
An example to illustrate both points above is: Abstract - "...the strength and weakness of Tai Chi compared to conventional PR, which is a superior modality of Tai Chi exercise..."
Please provide justification for anticipating a 20% drop-out rate (i.e. cite supporting research articles)
Author response: We have deleted or revised the inaccurate statements in the Strength, Abstract and main document to make the manuscript more precise such as following:
On Page 2: "Compare and contrast the feasibility and outcomes following three PR interventions (Tai Chi, TBRS, a combination of Tai Chi and TBRS) using a robust randomized controlled trial design and

methodology."
On Page 5: "Therefore, although either Tai Chi26-31 or conventional PR32 alone has been demonstrated to be beneficial to COPD, there are still many unknowns to better solve current clinical problems, such as how Tai Chi compares to conventional PR in terms of its pros and cons in COPD, if it is possible for Tai Chi to replace conventional PR, which modality of Tai Chi provides the maximal benefit to COPD patients, and how to compensate the limitation of conventional PR."
On Page 22: "Additionally, an exercise modality that integrates the components of mindfulness, breathing control and upper and lower extremities muscle training of Tai Chi and conventional PR will be examined."
Regarding to the bold statements about exploring the mechanism of Tai Chi exercise, it have also been revised and please refer to the Question No.14 of the third reviewer in the author response letter.
In RCTs, drop-out rate >20% poses serious threats to validity of the study.2,3 In this case, the loss can cause significant bias with mistrusting results and lead to failed RCT.2 Although a lower drop-out rate will lead to a smaller sample size, we estimate a 20% drop-out rate for this study to recruit more participants attempting to achieving the calculated sample size. We have added the citations as reference 21 and 22 on Page 9.

STRENGTH OF THE STUDY
3. Suggest limit the dot points to the main study strengths rather than including additional superfluous study characteristics. As an example, the first three dot-points could be combined to read as: "...Compare and contrast the feasibility and outcomes following three PR interventions using a robust RCT methodology..."
Author response: We have shortened the first three dot-points as the reviewer suggested on Page 2: "Compare and contrast the feasibility and outcomes following three PR interventions (Tai Chi, TBRS, a combination of Tai Chi and TBRS) using a robust randomized controlled trial design and methodology."

4. I feel the main strength in relation to dot-point 4 is the length of follow-up, so this information should be added here.
Author response: We have revised this as dot-point 2 on Page 2: "A long-term follow-up will be conducted after the supervised intervention, in which comprehensive types of exacerbations will be recorded, and the extended benefits of Tai Chi will be examined."

LIMITATIONS OF THE STUDY
5. One of the major limitations of this study will be the applicability to other populations, healthcare settings and cultural contexts where Tai Chi may not be as well established as it is in China.
Author response: As one of the traditional Chinese martial art, Tai Chi is well recognized and accepted in China. An increasing number of studies have emerged attempting to explore the role of Tai Chi in various diseases including COPD. Those well-designed studies have been completed in Australia, United State and UK etc., where there are also Tai Chi schools and communities for the practitioners. We agree with the reviewer that the applicability is a limitation of the Tai Chi study at this stage. The therapeutic effects of Tai Chi still need to be confirmed and applied in other populations. We have added this limitation as dot 4 on Page 2 and Page 23 in the Discussion as following: "The cultural contexts and healthcare settings might limit the applicability of Tai Chi in other countries and populations."

INTRODUCTION
6. I didn't feel that the authors provided sufficient rationale for incorporating and testing Tai Chi within the RCT intervention arm(s). Both Tai Chi and standard PR programs can be adapted to ensure flexibility with time and venue, cost-effective, and community or home-based; I would encourage the authors to scope the breadth/depth of literature around this (especially for standard PR programs). I

think a stronger argument could be the characteristics of Tai Chi which are not necessarily part of standard PR programs (i.e. mindfulness and incorporating functional movements with breathing control); this could be particularly beneficial for people with COPD where chronic sensations of dyspnoea are commonly an issue.
Author response: We agree with the reviewer that the rationale for incorporating Tai Chi within the intervention arms should be clarified, and appreciate the reviewer for providing a very good point for why assess the three interventions. We have scoped the related literature about Tai Chi and standard PR, and revised the rationale for testing Tai Chi within the intervention arms in the Discussion on Page 18-20 as following:
“Patients with COPD are characterised by the symptom of dyspnoea and by impaired exercise capacity. The chronic sensation of dyspnoea is one of the most common symptoms in COPD and is invariably present in all severity stages either at rest or under conditions of exercise. The mechanisms of dyspnoea and exercise intolerance in COPD are complex and multifactorial.34 Exercise capacity is often limited by dyspnoea, whereas exertional dyspnoea is partly reflecting peripheral muscle dysfunction.8 Exercise training is the best available means of improving muscle function in COPD and is considered the cornerstone of pulmonary rehabilitation.8 Pulmonary rehabilitation has been demonstrated clearly to improve the quality of life, reduce dyspnoea symptoms and increase exercise capacity in patients with COPD.33
It is known that a symptom is the individual's consciously appreciated sensation of a physiologic problem. A symptom is the result of an interaction of multiple physiologic, psychological, social, and environmental factors that affect the quality and intensity of the perception of the symptom.35 In COPD, strategies for the relief of dyspnoea can be physiologic or cognitive/behavioural. The rationale underlying the use of cognitive/behavioural strategies are that there is an interaction between the mind and body and that individuals can be taught new patterns of thinking, feeling, and behaving to cope with symptoms.36 A previous study has shown that yoga training was associated with significant symptomatic improvement of dyspnoea along with an improvement in exercise tolerance.37 Tai Chi is an ancient Chinese martial art and exercise; its inherent features of isometric exercise, stretching, relaxation and body posture correction combined with breathing techniques provide a typical mind-body exercise therapy for various diseases.28 An increasing number of studies attempt to explore the possibility of using this ‘old exercise’ for a ‘novel use’ in the treatment of COPD. The results appear to be quite promising; Tai Chi exercise has significant therapeutic effects on the improvement of the quality of life and exercise capacity and has an uncertain benefit on lung function based on several meta-analyses26,29,30 (Figure 3). However, the above conclusions are drawn only in comparison to non-physical exercise or breathing training that is mostly completed at home (Table 1). The benefits of Tai Chi might partially come from the muscle strength and balance exercises; however, the components of mindfulness and breathing techniques in Tai Chi, which are not a necessary part of standard PR might also contribute to the improvement in chronic dyspnoea. How Tai Chi compares to conventional PR in terms of improvement in patient-centred outcomes, including quality of life and severity of symptoms and other objective measures, is unknown (Figure 3). Therefore, in this study, we designed two parallel groups of Tai Chi and conventional PR to compare their effects in COPD. Conventional PR is characterised by exercise training to improve aerobic capacity and muscle strength. As one of the cognitive-behavioural therapies, Tai Chi exercise incorporates mindfulness and breathing control with functional movements. It is possible that the combination of these two exercises modalities would have complementary effects compared with exercise with Tai Chi or conventional PR alone on the clinical outcome of COPD including the severity of dyspnoea. The current study will examine the effect of an exercise modality incorporating Tai Chi in conventional PR on COPD outcomes.”

METHODS - DESIGN
7. The screening visit and run-in period is designed to provide participants with "education and training of both Tai Chi and TBRS exercise to exclude those who cannot tolerate the exercises and enhance study compliance". If you proceed with this approach, there are two major considerations

here:
(a) pre-selecting participants in this way will substantially skew your results towards populations who are 'healthier' and/or have a greater level of fitness - this will be a major limitation for your study (and should be documented as such)
(b) in clinical practice, PR programs are designed to be adaptable and accommodating of people regardless of their levels of physical fitness - again, this will be a major limitation to the applicability of your results/findings to clinical practice
Author response: We agree with the reviewer that the 'pre-selection' of participants will skew the study results to some extent. Previous studies have shown that PR is generally well tolerated in patients with severe COPD38,39 and even in those with very severe disease.40 In clinical setting, patients with COPD across all severity might be able to adapt to and benefit from PR program. However, the recruitment of the participants who cannot tolerate the exercise training in a clinical trial will definitely increase the drop-out rate and affect the study results, and also affect the safety of the study procedure. Given PR is well tolerated in different severity of patients with COPD, we deduce that fewer participants would be excluded, and the screening visit and run-in period is capable of increasing study compliance and safety. Despite this, the exclusion may still affect the external validity of study results. We agree that this is a limitation and have added in the manuscript on Page 23 as following: "CVD is among the most important comorbidities observed in COPD. We excluded COPD patients with symptomatic CVD for safety considerations, although studies show that patients with CVD benefit from rehabilitation programmes.28 Although previous studies have shown that PR is generally well tolerated in patients with severe COPD,38 patients with very severe lung function impairment and patients who are unable to tolerate the exercise during the screening and run-in period will be excluded based on the considerations of safety and compliance. The exclusion might affect the generalization of study results to populations in a 'real world' setting."

METHODS - SAMPLE SIZE
8. Based on the authors' calculations, in order to undertake four-group comparisons (and factoring in 20% drop-out) I would suggest that a larger sample size should be the aim (i.e. n>30, power 0.83) if it is within the project scope.
Author response: We agree with the reviewer that larger sample size may be aimed to ensure the study power. Based on our calculation, the recruitment of 25 to 30 participants would achieve a statistical power range from 0.74 to 0.83. The calculated number should be interpreted as how many participants should complete the study, therefore factoring in the 20% drop-out, the sample size should aim at 38 for each groups. [formula=30/(1-0.2), n=37.5] Therefore, we have submitted a revision of the study protocol to the 'Chinese Clinical Trial Registry' and IRB, and the revision has been approved.
The sample size was edited in the manuscript on Page 9 as following: "The sample size calculation of this study is based on the St. George Respiratory Questionnaire (SGRQ) total score in the study by Chan et al.4 By computing the changes in the SGRQ total score in the Tai Chi group and in the self-practice group (breathing and self-pacing walking exercise) before and after the interventions, 25 participants per group would be required to achieve a power of 0.8 and a significance level of 5% for difference detection. Furthermore, we conducted a power analysis using the fpower function in STATA 13.0 (Stata Corp., Tex., USA) to estimate the sample size needed to perform four-group comparisons provided that an alpha is set as 0.05. The results showed that a recruitment of 25 participants would achieve a statistical power of 0.74, and 30 participants would achieve a power of 0.83. A sample size of 38 participants per group, inclusive of a 20% dropout compensation,2,3 will be applied for this trial. Therefore, 38 participants per group and a total of 152 participants is a reasonable sample size for this study."

METHODS - MONITORING OF EXERCISE INTENSITY
9. Suggest that Borg PRE (which is a common PR measure of exercise intensity) should be included for use here as well. Participants who are prescribed beta-blockers may have a blunted

cardiovascular response to exercise.
Author response: We have searched the literature regarding the monitoring of exercise intensity before establishing the study protocol. Recent several studies have shown that Borg rating of perceived exertion (RPE) had a low validity to quantify the exercise intensity,41 and heart rate monitoring should be used for accurate intensity guidance.42 Therefore, we used heart rate to monitor the exercise intensity for different intervention groups. We agree with the reviewer that patients with COPD often have co-existing cardiovascular disease and may require beta-blocker treatments, which blunt the increase in heart rate in response to exercise. In this case, the Borg RPE may be used as an alternative approach to monitor exercise intensity. We have added this on Page 12 in the manuscript as following: "For individuals taking beta-blocker medications, the rate of perceived exertion using the Borg 6-20 scale will be applied to achieve target exercise intensity, and a score of 12 to 14 is categorised as moderate-intensity exercise.10"

METHODS - COPD RELATED EDUCATION
10. It is not clear whether all groups will receive education (i.e. protocol states only the control group will receive weekly education). Suggest this needs to be standardised across all groups.
Author response: Participants in the intervention groups will also receive the same disease related education as the control group. We have clarified this on Page 12 in the manuscript as following: "Participants in all four groups will receive the same weekly educational sessions. The contents include smoking cessation, diagnosis, COPD medications, action plan, exacerbations, nutrition, and self-management, such as infection prevention, inhalation technique, breathing and coughing techniques."

METHODS – OVERALL
11. What processes and procedures will be used to ensure Research Assistants (RAs)/Researchers are adequately qualified/trained to undertake outcome measurement/assessments? (i.e. certified Tai Chi instructor versus RAs for TBRS exercise who may/may not be experienced in PR).
Author response: As this is a single-blind trial, training sessions and outcome assessment will be conducted by the research physiotherapists, Tai Chi instructors and outcome assessors separately. For conventional PR, we collaborate with the staff working in the Department of Rehabilitation of the hospital that maintain a high level of proficiency and experience in PR. They will supervise the TBRS training. Tai Chi instructors each have experience of >10 years on conducting Tai Chi mind-body programme. We hold a GLP centre for traditional Chinese medicine in the hospital and in west China. Outcome assessors of the study are experienced research assistants working in the GLP centre who are certified in various COPD related questionnaires and tests, as well as the spirometry. A standard protocol and SOP will be established before the enrolment.
We have added the details about procedures to ensure qualified training and outcome assessments on Page 10 in the manuscript as following: "We will conduct training sessions with all the staff involved in the study including research physiotherapists for TBRS training, Tai Chi instructors and outcome assessors to thoroughly review the concepts of COPD and the standardized protocols for training and outcome assessments at the beginning of the study and as needed throughout the course of the study. All sessions will be monitored regularly and provide feedback throughout the study to ensure proper instruction."

12. How will you control for participants prior exposure/participation in PR programs and/or Tai Chi exercise? i.e. eligibility criteria for inclusion
Author response: Participants that involved in a PR program in the past 12 months, or those are currently practicing Tai Chi will be excluded from the study. We have clarified this in the exclusion criteria on Page 8 as following: "(5) participation in a PR programme in the past 12 months; and (6) currently practicing Tai Chi or participation in a clinical trials of COPD and other diseases."

13. Which staff will undertake PFTs? The detail regarding personnel involved, their level of

training/certifications etc. need to be included.
Author response: The outcome assessments including PFTs will be undertaken by the research assistants who have involved in a great number of clinical studies in our GLP centre with a high level of proficiency. We have added this in the manuscript on Page 13 as following: “PFTs will be undertaken by the outcome assessors that maintain a high level of proficiency and are certified to perform PFTs following the American Thoracic Society standards to assure optimal results.”

14. It is a bold aim to "explore the potential mechanisms of Tai Chi in COPD by addressing the level of systemic inflammation". Suggest the use of tempered (i.e. more passive) language here as there may be many other mechanisms by which Tai Chi and PR produce outcomes (i.e. other hormonal profiles, genetic factors etc.).
Author response: We have been aware of the bold statements of the mechanism, and have made the revisions accordingly as shown in the manuscript:
In the ‘Strength’ on Page 2: “We will explore the potential mechanisms of Tai Chi therapy related to systemic inflammation and immunity, which has not been addressed in previous Tai Chi studies of COPD.”
On Page 6: “The mechanisms underlying the therapeutic effects of Tai Chi in COPD are unknown. It is unclear if Tai Chi affects the level of systemic inflammatory markers in COPD that contribute to the clinical benefits from participating in Tai Chi.”
“(2) to explore the potential mechanisms of Tai Chi related to systemic inflammation and immunity in COPD.”
On Page 22-23: “We will examine the potential mechanism of different exercise modalities related to systemic inflammation and immunity; this topic was not addressed in previous Tai Chi studies of COPD.”

STATISTICAL ANALYSIS
15. Suggest that the authors need to consider detailing if/which multiplicity correction factor(s) will be applied.
Author response: We agree with the reviewer that multiplicity correction should be considered as there are multiple arms in the study. After the among-group statistical assessment, we will test for the pairwise comparisons between two intervention groups. According to Kim et al43, Tukey’s HSD procedure is considered as the most preferable method for the pairwise comparisons in this study. We have added this in the ‘Statistical analysis” on Page 16 in the manuscript as following: “Pairwise comparisons between the invention arms will be performed using Tukey’s HSD post hoc test.43”

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VERSION 2 – REVIEW

REVIEWER	Lei Pan Department of Respiratory and Critical Care Medicine, Binzhou Medical University Hospital, Binzhou 256603, China
REVIEW RETURNED	03-May-2016

GENERAL COMMENTS	The revised manuscript seemed to have been greatly improved than before.