Author's response to reviews

Title: Efficacy and safety of Qing-Feng-Gan-Ke Granules in patients with postinfectious cough: study protocol of a novel-design phase 3 placebo-controlled, double-blind randomized trial

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Author's response to reviews: see over
Dear Dr. Tom Rowles,

It is my honor to submit my manuscript to your journal. I had made a comprehensive revision for my manuscript titled *Efficacy and safety of Qing-Feng-Gan-Ke Granules in patients with postinfectious cough: study protocol of a novel-design phase III placebo-controlled, double-blind randomized trial* according to the comments reported by the two reviewers, Dr. Akio Niimi and Dr. Anne Elizabeth Vertigan. Their comments and suggestions were very inspiring and thought-provoking. All revisions are marked in red in the manuscript. I list my reply item by item as follow:

### (1) Reply to Dr. Akio Niimi

**Dear Dr. Akio Niimi,**

Firstly, I would thank you for reviewing my paper again. Your comments are really helpful. Secondly, I would like to say that I gave more information about the Chinese version of CQLQ in the manuscript and also provided the reference, which would help readers to know the questionnaire better. Thirdly, I would provide some detailed information that you requested for you.

The Chinese version of the CQLQ was created with adaptation of the cultural nuances in accordance with internationally published recommendations. Professor Irwin, the author of the original CQLQ, was contacted, and he granted the permission to produce the Chinese version of the CQLQ. Translation process included translation, back-translation, pre-testing techniques. The original CQLQ was translated into Chinese by two highly educated translators, a respiratory physician and a nonmedical person, separately. Both translators were native Chinese speakers and proficient in English. To reconcile the two Chinese versions of the CQLQ after translation, the two translators discussed the translations together. After producing a unanimous Chinese version of the CQLQ, two bilingual speakers (Chinese–English) without any background knowledge about the original CQLQ translated the Chinese version of the CQLQ into English together. After the back-translation, a committee consisting of two back translators and two forward translators and other four specialist pulmonary physicians reviewed and compared the back-translated version with the original version. The committee pointed out that some expressions in the back-translated version were not equivalent to those of the original one. To improve these expressions, the Chinese version was revised. Finally, outpatients who came to the clinic for the first time were interviewed face-to-face. They reviewed the revised Chinese version of the CQLQ and were asked whether they had any problems in understanding and answering the questions in revised Chinese version. 36 patients who were randomly selected were required to be re-tested using this questionnaire 24h later. After the pilot study, no further modification was needed. Therefore, the Chinese version of CQLQ was finalized.

A total of 86 cough patients were evaluated using Chinese version of CQLQ before treatment and two weeks post-treatment, and its reliability, validity and responsiveness were analyzed according to the results, after translation and cross-cultural adaptation of the original CQLQ into the Chinese language. Results The Cronbach's $\alpha$ coefficient and the 24 h test-retest reliability coefficient of the CQLQ were 0.935 and 0.931 respectively. The correlation coefficient between the scores of the four aspects (including physical complaints, psychosocial issues, functional abilities, and extreme physical complaints) and the total questionnaire score was high ($> 0.8$), but the coefficients of emotional well-being and personal safety fears were 0.536 and 0.540 respectively. Six common factors were extracted by the factor analysis which defined 66.603% of the full variation rates. The total score of questionnaire was up to 0.99 before and after treatment. It could be concluded according to the results above that CQLQ has good reliability and validity and can distinguish treatment effects well.

### (2) Reply to dear Dr. Anne Elizabeth Vertigan

**Dear Dr. Anne Elizabeth Vertigan,**

Thank you very much for your review. Your comments and suggestions are really helpful for me to improve my manuscript. I would reply to your comments point-by-point:

**Abstract**

1. Page 2: Third sentence under background. “Optimal treatment in western medicines for PIC has not been known.” This sentence should be changed. There is efficacy of Western medicine for this condition but he treatment effect is often incomplete.
I have changed the sentence.

2. **Page 2: Why is the upper age limit of 65 years used? Most other cough studies include older patients.**

Our protocol is implemented in strict accordance with good clinical practice (GCP) guidelines[34]. It is suggested that patients who are recruited in common clinical drug trials should be those aged between 18 and 65 years unless the trials are designed for younger or older group of people.

3. **Most patients with PIC will spontaneously resolve. The authors should include the influence of spontaneous recovery into the study design.**

Because of the self-healing tendency of PIC and lack of universally recognized therapy, we chose placebo as the control intervention. Furthermore, one of the meanings of the control group establishment in the RCT is to eliminate the influence of self-limiting character of disease. Randomization allocation, to a large degree, ensures the consistency(demographic characteristics, patient's disease condition, treatment history, compliance, et al.) between two groups. Although the curative effect in the treatment group will be overestimated as some patients recover without depending on intervention methods, the same thing also happens in patients in the control group.

**Background**

4. **There is a contradiction in saying that PIC can last for months but not more than 8 weeks (page 3).**

I am so sorry for the mistake. What I wanted to write is “but normally less than 8 weeks”.

5. **Can they authors define what they mean by a ‘meticulous job’? (Page 3)**

The “meticulous jobs” in my paper are jobs that require tremendous concentration and also elegant manner or voice. People with meticulous jobs in this manuscript including teachers, lecturers, radio announces and TV broadcasters, et al. As this phrase was confusing and would puzzle readers we made some changes in this part.

6. **The description of PIC as intractable does not seem accurate if it only lasts for less than 8 weeks.**

PIC is supposed to be the most common cause of subacute cough, which is distinguished from the chronic cough by the duration of coughing. For adults, retrospective studies of unselected patients with a history of upper respiratory tract infection showed that the frequency of PIC ranged from 11 to 25%, which increased to the range from 25 to 50% during outbreaks of atypical pathogens infections. Although PIC dose not persist for a very long time, and it is self-limited and will usually resolve on its own in time, one-month period of cough always incurs troubles for patients and their surroundings in their daily life. Moreover, because of a lack of effective treatment methods, patients would try a variety of treatments which would result in economic costs. I could understand your doubt so I deleted the word “intractable” as it might be an exaggerated expression.

7. **The term general care needs to be defined (page 4).**

I have revised the sentences.

8. **References need to be provided for quality of life (page 4).**

I have added the reference.

9. **Examples of adverse outcomes should be provided (page 4).**

I have supplemented some examples of the adverse outcomes.

10. **A description of the bias in previous studies should be provided.**

The previous phase 2 clinical trial has been accepted by Chinese Medicine, a peer-reviewed SCI journal and will be published online soon. I supplemented some information about bias of phase 2 trial in my revision.

There is also an absence of objective measurements in phase 2 study. Moreover, in phase 2 study, only those patients whose total cough symptom score is not 0(still cough) at visit 2 would be followed up, which would result in an exaggerated effect of the study drug because that cough would happen again within 24 hours in some patients. In the current phase 3 study, we would conduct a two-day follow up to avoid this bias.

11. **More information is needed on the integral syndrome differentiation, particularly for readers who are unfamiliar with TCM (page 4). How does the health practitioner arrive at the syndrome differentiation.**

All personnel involved in this trial will be trained prior to trial initiation. Training program is about study protocol and relevant skills, especially the skill of TCM syndrome differentiation. I gave the TCM “pathogenic-wind invading lung syndrome” diagnostic criteria in table 4. Patients who satisfy the primary symptom and the first item of secondary symptoms as well as specific
tongue picture and pulse condition could be differentiated as “pathogenic-wind invading lung syndrome”. TCM syndrome diagnostic criteria is designed based on State Administration of Traditional Chinese Medicine guidelines[27].

TCM integral syndrome differentiation is a complex system. I could only add a brief introduction in my protocol because of the word number limit. I believe that if some readers are interested in TCM, they would learn this ancient medicine from other professional learning materials. I would like to give a detailed introduction for you here.

TCM, one of China's splendid cultural heritages, is the science dealing with human physiology, pathology, diagnosis, treatment and prevention of diseases. TCM summed up the experience of the Chinese people in their long struggle against diseases and, under the influence of ancient naive materialism and dialectics, evolved into a unique, integral system of medical theory through long clinical practice. The formation of the theoretical system of TCM was greatly influenced by ancient Chinese materialism and dialectics. The theoretical system takes the physiology and pathology of zang-fu organs and meridians as its basis, and Treatment by Differentiation of Syndrome(TDS) as its diagnostic and therapeutic features. Differentiation means comprehensive analysis, and syndrome refers to symptoms and signs. Differentiation of syndromes implies that the patient's symptoms and signs collected by the four diagnostic methods(inspection, auscultation ant olfaction, inquiry, pulse-taking and palpation) are analyzed and summarized so as to identify the etiology, nature and location of a disease, and the relationship between vital qi and pathogens, thereby determining what syndrome the disease belongs to. By treatment it means that selecting the corresponding therapy according to the outcome of differentiating syndromes. Taken as a whole, TDS means diagnosis and treatment based on overall analysis of symptoms and signs.

12. Page 4 paragraph 2: The phrase “which proved the antitussive and...”should be changed to “which suggests antitussive and...”. Also “subsequent clinical studies underpinned”should be changed to “subsequent clinical studies investigated”.

I have changed the words according to your suggestions.

13. A reference should be provided for the last sentence in paragraph 2 page 4.

Reference of phase II study, which was not published yet(just in press), was added.

Study design

14. How will the symptom differentiation be determined? How consistent are the researchers in making this determination? What criteria is used in making this assessment?

The “pathogenic-wind invading lung syndrome” diagnostic criteria were explained in table 4. This diagnostic criteria was followed the guideline published China Press of Traditional Chinese Medicine[27].

Indeed, TCM symptom differentiation, to some degree, inevitably involves the subjective perceptions of physicians. Different physicians would classify the disease condition of the same patients as different TCM syndrome style. In order to ensure the consistency of symptom differentiation from different physicians, all of the physicians who take part in symptom differentiation would receive professional training about this skill. After the training sessions, we also have conducted a pilot study to explore the consistency problem of discriminating “TCM syndrome”. The decision tree classifier is used as a tool and the rate of classification accuracy is used to measure the consistency. A small set of PIC data(data of 30 PIC outpatients) is analyzed by 6 physicians who were selected randomly from 6 participating center. We found that rates of classification accuracy are satisfying(>0.9), which implies a good consistency in discriminating TCM symptom between physicians.

15. The description of table 1 in the text does not seem to match the content of table 1. Table 1 actually lists the inclusion and exclusion criteria for participants in the study.

I am so sorry for the mistakes. I have corrected the Table number and description.

16. Who will assess the patients? Are the staff assessing the patients different from the staff providing the treatment.

Yes. Physicians will assess the patients while assistant researchers are responsible for drug delivery.

Participants

17. It would be better to separate the description of the participants from the methodology and study design.

I have readjusted the content.

18. The content of tables 2 and 3 do not match the description in the text.
I have corrected the mistakes.

19. Page 6: The four time points need to be explained in the text.
I supplemented simple information about four time-points in the parentheses which would help readers to find out the corresponding time in the table.

20. Page 6: “As long as a little bit difference is observed”. This needs to be more specific.
I made revisions.

21. How will the participants be recruited for the study? Who will approach the patients?
Until the required quota of participants is reached, all potential patients can join in this trial through two ways, advertisement and review of health records by respiratory physicians. Advertisement will be posted on the bulletin board of the participating hospitals by assistant researchers and all of the participants will be interviewed and contacted by respiratory physicians.

Randomization and blinding

22. Blinding needs to be better described. A flowchart might help to outline the process.
A flowchart was attached (Fig.1).

23. Stratification needs to be explained in more detail. What is stratification to be based on?
We used a stratified randomization method, with stratification by participating center. The random coding of each center was produced using Statistics Analysis System (SAS) software.

24. It is unclear whether the researchers will know what group the patient is in.
No. A specific group of research assistants who are independent of recruitment, intervention or assessment of outcomes would prepare the envelopes, which contains the information about intervention group. Other researchers would not know which group the patient is in. I have clearly explained this in my revised manuscript.

25. Will the placebo medication be matched for taste?
Yes, the placebo were designed and manufactured to resemble the taste, smell and appearance of QFGKG. I have replenished this information in the revision.

26. If the code is broken will the treating Dr know?
Yes. Exceptional circumstance under which unblinding is permissible is when knowledge of intervention is absolutely necessary for further management, for example, if an unpredictable severe harm happens to a patient, the chief investigator is qualified to open the emergency envelope and guide physicians (the treating doctors) to treat the patient according to emergency measures. The patient must be withdrawn and be followed up until he/she recovers. In this case, the chief investigator should report the case to hospital ethical committee and drug administration agency. The broken code and reasons for unblinding should be recorded on the case report form (CRF). Meanwhile, severe adverse event report form (SAERF) will also be completed. During the revealing, allocation information must not be disclosed to the patient and any third party.

Intervention

27. Figures 1 and 2 are tables rather than figures.
I have changed the words.

28. Two day follow up is not sufficient. Follow up should be at least one month later.
The follow up period is indeed short. However we just want to know whether the cough would be resolved on visit 2 because that QFGKG is supposed to be an antitussive with fast effect.

29. What are the physical properties of the QFGKG?
I am so sorry for the missing of this information. I have contacted the manufacturer of QFGKG, Baotou TCM Co., Ltd. However, I am afraid that I can not provide more information about physical properties of the QFGKG because the manufacturer would publish these contents including solubility, stability, melting point, volatile, hygroscopic and differentiation of this drug in the near future by themselves.

Outcomes

30. Is the outcome for section A to determine the difference between treatment and placebo groups?
Yes.

31. More information is needed about the cough symptom score. Is it a questionnaire completed by the patient? Is it obtained in an interview? Does the health practitioner complete it on behalf of the patient?
Cough symptom score scale is showed in Table 6. The patients give their cough severity at daytime and nighttime a score by themselves in an interview at visit.

32. More information is needed about the TCM symptom score.
The TCM symptom score system used in the study follows the Guidelines for Clinical Research of New Chinese Medicine[26], in which all symptoms are given graded scores (Figure 2). TCM signs will also be assessed, but not scored. The sum of all symptom scores is the cumulative TCM symptom score. The change in cumulative TCM symptom score is assessed by the percentage of symptom score reduction (PSSR), which is calculated according to the following formula:

\[
\text{PSSR} = \left( \frac{\text{Cumulative symptom score before treatment} - \text{Cumulative symptom score after treatment}}{\text{Cumulative symptom score before treatment}} \right) \times 100\%
\]

### Figure 2: TCM symptom score and TCM signs

#### TCM symptom

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary symptom</strong></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>0  2  4 6</td>
</tr>
<tr>
<td>Throat itching</td>
<td>0  1  2 3</td>
</tr>
<tr>
<td>Cough sensitivity to cold air, heat air or strange odors</td>
<td>No  Yes</td>
</tr>
<tr>
<td>Nonproductive cough</td>
<td>No  Yes</td>
</tr>
<tr>
<td>Dry throat</td>
<td>None  Mild  Moderate  Severe</td>
</tr>
<tr>
<td>Chest stuffiness</td>
<td>None  Mild  Moderate  Severe</td>
</tr>
<tr>
<td><strong>Secondary symptom</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cumulative symptom score</strong></td>
<td></td>
</tr>
</tbody>
</table>

#### TCM signs

<table>
<thead>
<tr>
<th>Symptom</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tongue proper</td>
<td>□ Slight red □ Red tip □ Other:</td>
</tr>
<tr>
<td>Tongue coating</td>
<td>□ White □ Yellow □ Other:</td>
</tr>
<tr>
<td>Pulse condition</td>
<td>□ Normal □ Floating □ Other:</td>
</tr>
</tbody>
</table>

33. **What about patient self report of side effects?**
Self reported side effects will be recorded in the CRFs(Case Report Forms). I added this information in the manuscript.

34. **No objective cough measures have been included.**
I have to admit the absence of objective cough measurements in our study and I also added this limitation in the Discussion section. Many video and sound recording surveillance have been used in clinic to objectively monitor the cough frequency and severity[1,7,10,11]. However some studies reported a poor relationship between cough frequency and cough symptom score[7,10,11]. Moreover, comprehensive cough monitoring is not a simple task. Firstly, although operating a manual recording instrument is easy for patients, it requires a good compliance. Otherwise, considerable errors could be induced. Secondly, how to effectively and sensitively distinguish and filter the external vocal interference, and also record the weak electromyographic signals of pulmonary muscles are still the technical bottlenecks for the development of 24h cough monitors. Thirdly, the expensive cost also limits the use of cough recording surveillance. For the above reasons, we did not include an objective cough measurement.

**Statistical Analysis**

35. **Who will equivalence at baseline between the two groups be ensured?**
A group of professional statisticians who are independent of all the other process of the study would perform the statistical analysis including the baseline equivalence analysis.

**Ethics**

36. **Page 11 –It is unclear what the authors mean by ‘contentment.’**
It means “satisfaction”. It patients have any questions about the protocol, physicians should give a full explanation(a satisfying response to all questions from patients) until they understand it completely.

37. **Page 11 –Change ‘working on to verify and extend’ to ‘studying’**
The words have been changed.

**Discussion**

38. **Page 11 –change great to some.**
It has been changed.
39. The authors need to comment on the extent to which this methodology has been used in other cough research.
Actually, this methodology has not been used in other researches. This is just a tentative trial in an attempt to provide some practical information about this method.

40. Page 12: The sentence ‘Although they are independent for settling different questions....’
Is not a complete sentence and the meaning is unclear.
The sentence has been modified.

41. Page 12: “has been first proposed.....”The meaning of this sentence is unclear.
It has been modified.

42. Page 12: First sentence of the last paragraph needs to be more succinct.
It has been modified.

Tables and figures
43. Table 1
a. Are other serious causes ruled out?
Yes. This information were explained in Table 2. Causes that would be ruled out including disorders that could result in cough (upper airway cough syndrome, cough variant asthma, eosinophilic bronchitis and gastroesophageal reflux disease), severe pulmonary diseases such as COPD, lung cancer, pulmonary tuberculosis and also hypertension that involves the use of angiotensin converting enzyme inhibitor (ACEI).
b. How is post infectious cough determined?
Post infectious cough diagnostic criteria were listed in Table 2.
c. Are patients with psychiatric disorders excluded if the disorders are current or if there is any history.
As long as patients have a history of psychiatric disorders, they would be excluded from this study.
d. What does legal disability mean?
It means a legal impediment to taking a certain action, such as being a minor who cannot legally enter into a contract.

44. Table 2
a. Why is the tongue condition relevant?
Traditional Chinese medicine (TCM) includes a range of traditional medical practices originating in China. It is considered a Complementary or Alternative Medical system in much of the western world while remaining as a form of primary care throughout most of Asia. In diagnosis, TCM takes the four diagnostic methods, inspection, auscultation ant olfaction, inquiry, pulse-taking and palpation as its principal techniques. Tongue(tongue proper and tongue coating) inspection is one major part in inspection process as tongue condition helps to identify the etiology, nature and location of a disease.

45. Table 4
a. Does baseline balance test mean baseline patient characteristics?
Yes. Quantitative outcomes including age, disease duration, body temperature, heart/respiratory rate, blood pressure and qualitative outcomes including gender, marriage, race, previous history(Table 7).
b. Gender and previous treatment should also be included.
Gender and previous treatment are included in baseline balance test.
c. What does ‘history’ mean.
‘History’ means treatment history.
d. More information about the CQLQ is needed including the translation.
More information about the CQLQ was supplemented.
The Chinese version of the CQLQ was created with adaptation of the cultural nuances in accordance with internationally published recommendations. Professor Irwin, the author of the original CQLQ, was contacted, and he granted the permission to produce the Chinese version of the CQLQ. Translation process included translation, back-translation, pre-testing techniques using. The original CQLQ was translated into Chinese by two highly educated translators, a respiratory physician and a nonmedical person, separately. Both translators were native Chinese speakers and proficient in English. To reconcile the two Chinese versions of the CQLQ after translation, the two translators discussed the translations together. After producing a unanimous Chinese version of the
CQLQ, two bilingual speakers (Chinese–English) without any background knowledge about the original CQLQ translated the Chinese version of the CQLQ into English together. After the back-translation, a committee consisting of two back translators and two forward translators and other four specialist pulmonary physicians reviewed and compared the back-translated version with the original version. The committee pointed out that some expressions in the back-translated version were not equivalent to those of the original one. To improve these expressions, the Chinese version was revised. Finally, outpatients who came to the clinic for the first time were interviewed face-to-face. They reviewed the revised Chinese version of the CQLQ and were asked whether they had any problems in understanding and answering the questions in revised Chinese version. 36 patients who were randomly selected were required to be re-tested using this questionnaire 24h later. After the pilot study, no further modification was needed. Therefore, the Chinese version of CQLQ was finalized.

A total of 86 cough patients were evaluated using Chinese version of CQLQ before treatment and two weeks post-treatment, and its reliability, validity and responsiveness were analyzed according to the results, after translation and cross-cultural adaptation of the original CQLQ into the Chinese language. Results The Cronbach’s $\alpha$ coefficient and the 24 h test-retest reliability coefficient of the CQLQ were 0.935 and 0.931 respectively. The correlation coefficient between the scores of the four aspects (including physical complaints, psychosocial issues, functional abilities, and extreme physical complaints) and the total questionnaire score was high (> 0.8), but the coefficients of emotional well-being and personal safety fears were 0.536 and 0.540 respectively. Six common factors were extracted by the factor analysis which defined 66.603% of the full variation rates. The total score of questionnaire was up to 0.99 before and after treatment. It could be concluded according to the results above that CQLQ has good reliability and validity and can distinguish treatment effects well.

**46,47,48 Grammars, verbal expressions, sentence structures, and vocabularies**

We have extensively refined the language followed all your suggestions and also with some help from a native English speaker.

Sincerely,

Wei Liu (the first author)