PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Sipjeondaebo-tang in cancer patients with anorexia: a protocol for a pilot, randomised, controlled trial
AUTHORS	Cheon, Chunhoo; Park, Sunju; Park, Yu Lee; Huang, Ching-Wen; Ko, Youme; Jang, Bo-Hyoung; Shin, Yong-Cheol; Ko, Seong-Gyu

VERSION 1 - REVIEW

REVIEWER	Byung-Cheul Shin Pusan National University, South Korea
REVIEW RETURNED	12-Feb-2016

GENERAL COMMENTS	In this manuscript, the authors planned a randomized, placebo-controlled, clinical trial which tested the efficacy and safety of Sipjeondaebo-tang for patients with cancer anorexia to determine whether sipjeondaebo-tang treatment would be effective in improving anorexia for cancer patients. This study protocol seems generally well designed and is following recommended current reporting guideline of SPIRIT or ethical clinical trial procedure with reasonable manner. However it has several points should be addressed or discussed for improving the quality with balanced view points. 1. Main concern is whether it is a pilot study or not. If it is a pilot RCT, your research aim is not to explore the efficacy and safety of Sibjeondaebo-tang but to test the feasibility to go to main RCT. Therefore your research aim(s) should be changed by your objective research design. If it is a confirmatory RCT, please supply exact sample size to confirm the efficacy & safety of Sibjeondaebo-tang in page 6. - I recommend your title as “Sipjeondaebo-tang in cancer patients with anorexia: a protocol for a pilot, randomised, controlled trial” as recommended by SPIRIT. 2. Another main concern is that, for SPIRIT checklist, many items were answered as NA, but should be clearly reported by adding more detailed information. 3. Please check tense agreement through the manuscript. - “The outcomes are measured on every visit. Each subject will visit once a week during 4 weeks.” -> “The outcomes will be measured on every visit. Each subject will visit once a week during 4 weeks” in page 2 - “They would orally take 3 grams of granules with water three times a day after meals for 4 weeks.” -> “They will orally take 3 grams of granules with water three times a day after meals for 4 weeks” in page 7.

	4. I am not able to grasp why the random number table be provided to the Pharm and foods company. What's the reason the herbal company be announced the random number? 5. Please supply the reason why the dosage of SJDBT is 3 grams*3 per day in page 7. Additionally, the sentence indicates that the total of "a compound of Cinnamomi Cortex 1.00g, Paeoniae Radix 1.00g, Atractylodis Rhizoma Alba 1.00g, Ginseng Radix Alba 1.00g, Cnidii Rhizoma 1.00g,Astragali Radix 1.00g, Poria Sclerotium 1.00g, Rehmanniae Radix Preparata 1.00g,Angelicae Gigantis Radix 1.00g and Glycyrrhizae Radix 0.5g" makes 9.5g. Does it indicate 9.5g/day? All descriptions of dosage are unclear or mismatched. 6. Please check your manuscript following the reporting guideline of CONSORT 25 items [1]. Even though your protocol follows study protocol reporting guideline of SPIRIT, when you report your results, CONSORT reporting guideline will be helpful for your future submission of your final results. [1] http://www.consort-statement.org/ 7. For the description of placebo, did you test whether participants/or patients were not able to discriminate the difference between real herbal medicine and placebo? 8. There is scare information about assessor blinding and allocation concealment. 9. Did you use all outcome measurement tools were validated or equally translated in Korean version? As an example, a validated Korean version of anorexia-cachexia subscale of FAACT should be used. How about 'Qi deficiency and blood deficiency scale'? Please give additional information of validation of outcomes as reference(s) to related sentences in page 8. 10. Table 1 should be revised following SPIRIT recommendation. 11. Please supply whether patients will be protected by being covered with insurance or not. 12. in the section of statistical analysis in page 10, - Please add basic information of statistics. P value will be set at 0.05?, two tailed? Minor comments 1. [16][17] in page 4 -> [16,17] 2. '…in Korean patients with cancer' in page 4-> '… in Korean cancer patients' 3. Several references attached to referenced sentences are not fit for referenced sentences. E.g.) reference 2 in page 3, reference 9 in page 3 4. Please describe more in depth about advertisement used in the section of 'Recruitment' in page 5. 5. Please check abbreviations with consistency in main text. Define it at the first appearance, then use it after the definition. E.g.) ECOG in page 5, etc. 6. I am not able to understand the meaning of the sentence of 'patient who reports more than 7 points of Numeric Rating Scale

	within 2 weeks of screening which can affect appetite or calorie intake' in page 5. 7. student's t-test -> independent t-test in page 10

REVIEWER	Chen, Huang-Chi Graduate Institute of Integrated Medicine, China Medical University, Taiwan Yuanlin Christian Hospital, Taiwan
REVIEW RETURNED	13-Feb-2016

GENERAL COMMENTS	1. For a pilot study, relatively small sample size is acceptable. However, there are still some limitations worthy of mentions. This investigation focus on patients with cancer. However, different types of cancers are associated with different gastrointestinal presentations. For example, patients with lung cancer may have quite different presentation when compared with patients with rectal cancer. In addition, different stage of certain type of cancer may lead to different severity of anorexia. For example, stage I gastric cancer patients would have relatively mild anorexia when compared with terminal stage patients. 2. In the inclusion criteria, "individuals who are suffering from cancer-associated anorexia" would be enrolled. Would you further explain and how to define "cancer-associated anorexia"? How could we confirm the cause of anorexia to be cancer rather than other problems, such as depression, drugs, ...etc? 3. In the exclusion criteria, "patient who survives at least 5 years after cancer diagnosis" is excluded. Would you further explained the reason in the discussion or other part in the manuscript.

VERSION 1 – AUTHOR RESPONSE

To Reviewer 1

Thank you very much for your kind comments and suggestions on our manuscript. We have modified the manuscript accordingly, and detailed corrections are listed below point by point. The comments and suggestions are valuable and very helpful for revising and improving our manuscript.

1. Main concern is whether it is a pilot study or not.

If it is a pilot RCT, your research aim is not to explore the efficacy and safety of Sibjeondaebo-tang but to test the feasibility to go to main RCT. Therefore your research aim(s) should be changed by your objective research design. If it is a confirmatory RCT, please supply exact sample size to confirm the efficacy & safety of Sibjeondaebo-tang in page 6.

- I recommend your title as "Sipjeondaebo-tang in cancer patients with anorexia: a protocol for a pilot, randomised, controlled trial" as recommended by SPIRIT.

Response

Thank you for your comment and suggestion. The title "Sipjeondaebo-tang in cancer patients with anorexia: protocol for a randomised, controlled trial" has been changed into "Sipjeondaebo-tang in cancer patients with anorexia: a protocol for a pilot, randomised, controlled trial". Also aim of the present study has been changed into 'test the feasibility for a full randomized clinical trial' in the abstract and main text.

2. Another main concern is that, for SPIRIT checklist, many items were answered as NA, but should be clearly reported by adding more detailed information.

Response

Thank you for your comment and suggestion. We have added every possible information according to SPIRIT checklist in revised manuscript. We have attached revised SPIRIT checklist.

3. Please check tense agreement through the manuscript.
- “The outcomes are measured on every visit. Each subject will visit once a week during 4 weeks.” -> “The outcomes will be measured on every visit. Each subject will visit once a week during 4 weeks” in page 2
- “They would orally take 3 grams of granules with water three times a day after meals for 4 weeks.” -> “They will orally take 3 grams of granules with water three times a day after meals for 4 weeks” in page 7.
Response
Thank you for your comment and suggestion. We have corrected tense agreement you have pointed out.
- “The outcomes are measured on every visit. Each subject will visit once a week during 4 weeks.” -> “The outcomes will be measured on every visit. Each subject will visit once a week during 4 weeks” in page 2
- “They would orally take 3 grams of granules with water three times a day after meals for 4 weeks.” -> “They will orally take 3 grams of granules with water three times a day after meals for 4 weeks” in page 8.
- “Thus, in this study, we would evaluate efficacy of SJDBT, an herbal medicine consisting of ten herbs that are known to be beneficial to strengthen the body after illness and treat anorexia.” -> “Thus, in this study, we will evaluate efficacy of SJDBT, an herbal medicine consisting of ten herbs that are known to be beneficial to strengthen the body after illness and treat anorexia.” In page 13

4. I am not able to grasp why the random number table be provided to the Pharm and foods company. What’s the reason the herbal company be announced the random number?
Response
Thank you for your comment and suggestion. When the experimental products are produced, packaging and labelling will be done in production process. In order to distinguish Sipjeondaebo-tang and placebo in the process, random number table will be provided to the pharmaceutical company. We have added following sentence in page 7 for a detailed description: “The experimental products will be produced and labelled using the randomisation numbers at the Hanpoong Pharm and Foods Co., Ltd., the pharmaceutical company. For this procedure the random number table will be provided to the pharmaceutical company.”

5. Please supply the reason why the dosage of SJDBT is 3 grams*3 per day in page 7. Additionally, the sentence indicates that the total of “a compound of Cinnamomi Cortex 1.00g, Paeoniae Radix 1.00g, Atractylodis Rhizoma Alba 1.00g, Ginseng Radix Alba 1.00g, Cnidii Rhizoma 1.00g,Astragali Radix 1.00g, Poria Sclerotium 1.00g, Rehmanniae Radix Preparata 1.00g,Angelicae Gigantis Radix 1.00g and Glycyrrhizae Radix 0.5g” makes 9.5g. Does it indicate 9.5g/day? All descriptions of dosage are unclear or mismatched.
Response
Thank you for your comment and suggestion. In the present study we followed MFDS(Ministry of Food and Drug Safety)-recommended dosage of SJDBT, 3 grams*3 times per day.
We missed some explanation about drug production process. The mentioned dosage is doses of raw materials before extraction and concentration process for single dose 3 grams.
We have added following sentence in page 8 for a supplementary explanation: “The daily doses follows Ministry of Food and Drug Safety(MFDS)-recommended dosage and administration of SJDBT.”, “These raw materials will be extracted, concentrated to 3 grams for single dose.”

6. Please check your manuscript following the reporting guideline of CONSORT 25 items [1]. Even though your protocol follows study protocol reporting guideline of SPIRIT, when you report your

results, CONSORT reporting guideline will be helpful for your future submission of your final results.
[1] http://www.consort-statement.org/
Response
Thank you for your comment and suggestion. We have checked our manuscript following the reporting guideline of CONSORT 25 itmes and have attached CONSORT checklist. Because this manuscript is study protocol, some items related results of the study has remained NA.

7. For the description of placebo, did you test whether participants/or patients were not able to discriminate the difference between real herbal medicine and placebo?
Response
Thank you for your comment and suggestion. To our regret, we did not test whether participants were able to discriminate the difference between real herbal medicine (SJDBT) and placebo for this study. However, we conducted clinical trials using same formulation placebo from same pharmaceutical company (Hanpoong Pharm and Foods Co.) such as Taeumjowi-tang extract, Euiiin-tang extract. In the previous studies, it is empirically confirmed that participants could not discriminate between placebo and real herbal medicine.

8. There is scare information about assessor blinding and allocation concealment.
Response
Thank you for your comment and suggestion. We have added following sentence in page 7 for more detailed explanation: “A research assistant who are not involved in recruitment, intervention or assessment of outcomes will prepare the envelopes. Investigators responsible for recruitment and assessment is not allowed to take part in the group allocation.

9. Did you use all outcome measurement tools were validated or equally translated in Korean version? As an example, a validated Korean version of anorexia-cachexia subscale of FAACT should be used. How about ‘Qi deficiency and blood deficiency scale’? Please give additional information of validation of outcomes as reference(s) to related sentences in page 8.
Response
Thank you for your comment and suggestion. Functional Assessment of Cancer Therapy (FACT) questionnaire series are widely used, validated and officially translated measurement tools. However, Qi deficiency and blood deficiency scale are not yet validated like most measurement tools of oriental medicine. We hope that this pilot study could encourage validation study on those tools. We have added following sentence in page 8, 9 for more detailed explanation: “Korean translation version of FAACT which is produced by the FACIT organization will be used”, “Korean translation version of FACT-G is validated and Qi deficiency and blood deficiency scale translated by the Korean expert”

10. Table 1 should be revised following SPIRIT recommendation.
Response
Thank you for your comment and suggestion. Table 1 has been revised following SPIRIT recommendation in page 9, 10.

11. Please supply whether patients will be protected by being covered with insurance or not.
Response
Thank you for your comment and suggestion. We have added following sentence in page 11: “Any loss caused by the trial will be reimbursed by insurance.”

12. in the section of statistical analysis in page 10,
- Please add basic information of statistics. P value will be set at 0.05?, two tailed?
Response
Thank you for your comment and suggestion. We have added following sentence in page 11 for more detailed explanation: “A two-sided, 5% or lower p-value will be considered statistically significant.”

Minor comments
1. [16][17] in page 4 -> [16,17]
Response
Thank you for your comment and suggestion. “[16][17] “ has been changed into “[16,17]”

2. ‘…in Korean patients with cancer’ in page 4-> ‘… in Korean cancer patients’
Response
Thank you for your comment and suggestion. “… in Korean patients with cancer” has been changed into “… in Korean cancer patients”

3. Several references attached to referenced sentences are not fit for referenced sentences.
E.g.) reference 2 in page 3, reference 9 in page 3
Response
Thank you for your comment and suggestion. There’s been a mix up with reference.
Reference 2 has been changed into “Bruera E. Clinical management of anorexia and cachexia in patients with advanced cancer. Oncology. 1992;49 Suppl 2:35-42”
“… is recently known to have the potential antiemetic effect“ has been changed into “… is recently known to have the potential effect of antiemetic and ameliorates cancer-induced anorexia and cachexia” in page 3.

4. Please describe more in depth about advertisement used in the section of ‘Recruitment’ in page 5.
Response
Thank you for your comment and suggestion. “Detailed information on the trial is posted on bulletin board at the hospital, and the patients who see the board will voluntarily visit the trial site.” has been changed into “Detailed information on the trial including study period, purpose of study, inclusion and exclusion criteria, and intervention is posted on bulletin board at the hospital, and the patients who see the board will voluntarily visit the trial site.”

5. Please check abbreviations with consistency in main text. Define it at the first appearance, then use it after the definition.
E.g.) ECOG in page 5, etc.
Response
Thank you for your comment and suggestion. We checked abbreviations through the manuscript. Abbreviation of “Sipjeondaebo-tang” has been defined in page 3 and that of “Eastern Cooperative Oncology Group” has been defined in page 6.

6. I am not able to understand the meaning of the sentence of ‘patient who reports more than 7 points of Numeric Rating Scale within 2 weeks of screening which can affect appetite or calorie intake’ in page 5.
Response
Thank you for your comment and suggestion. There had been some unnecessary words and a missing word. The sentence has been changed into “patient who reports more than 7 points of Numeric Pain Rating Scale”

7. student’s t-test -> independent t-test in page 10
Response
Thank you for your comment and suggestion. “a student’s t-test” has been changed into “an independent t-test” in page 11.

To Reviewer 2

Thank you very much for your kind comments and suggestions on our manuscript. We have modified the manuscript accordingly, and detailed corrections are listed below point by point. The comments and suggestions are valuable and very helpful for revising and improving our manuscript.

1. For a pilot study, relatively small sample size is acceptable. However, there are still some limitations worthy of mentions. This investigation focus on patients with cancer. However, different types of cancers are associated with different gastrointestinal presentations. For example, patients with lung cancer may have quite different presentation when compared with patients with rectal cancer. In addition, different stage of certain type of cancer may lead to different severity of anorexia. For example, stage I gastric cancer patients would have relatively mild anorexia when compared with terminal stage patients.
Response
Thank you for your comment and suggestion. To our regret, we couldn't consider different types and stages of cancer as focusing anorexia of cancer patients and considering feasibility of conducting the trial. We hope that we are able to conduct further study considering these things based on the present pilot study. We have added following sentence in page 14 for a detailed description:
"However this study also has limitations mostly stemming from that it has relatively small sample size and is a single-centre pilot trial. The present study focuses on Qi deficiency and blood deficiency which are all included in prescription criteria of SJDBT as well as anorexia. Considering recruitment feasibility, different types and stage of cancer patients will be recruited, then characteristics of each type and stage is difficult to detect. Further studies are needed to assess the influence of specific type and stage of cancer."

2. In the inclusion criteria, "individuals who are suffering from cancer-associated anorexia" would be enrolled. Would you further explain and how to define "cancer-associated anorexia"?
How could we confirm the cause of anorexia to be cancer rather than other problems, such as depression, drugs, ...etc?
Response
Thank you for your comment and suggestion. There's been a mix up with inclusion criteria. "individuals who are suffering from cancer-associated anorexia" has been changed into "individuals who are suffering from anorexia" in page 5.
As you commented, it is practically difficult to confirm the cause of anorexia to be cancer. So, we will include cancer patients with anorexia, but without depression, severe pain which can influence on appetite. Therefore, we have added following sentence discussion section in page 13: "It is practically difficult to confirm whether the cause of anorexia is cancer or not. Thus the present study will recruit every cancer patient who has anorexia, but exclude participants who have disease or symptom, which can influence on appetite, such as depression, pain, and hypoadrenalism."

3. In the exclusion criteria, "patient who survives at least 5 years after cancer diagnosis" is excluded. Would you further explained the reason in the discussion or other part in the manuscript.
Response
Thank you for your comment and suggestion. Though it is not enough, for not to recruiting too diverse participants, we will exclude patients who survives at least 5 years after cancer diagnosis. We have added following sentence discussion section in page 14: "For recruiting participants who are currently suffering from cancer, patients who survives at least 5 years after cancer diagnosis will be excluded."