PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and safety of the Shexiang Baoxin pill for the treatment of coronary artery disease not amenable to revascularization: Study protocol for a randomised, placebo-controlled, double-blinded trial
AUTHORS	Tian, Panpan; Li, Jun; Gao, Jian; Li, Ying

VERSION 1 – REVIEW

REVIEWER	Raina MacIntyre UNSW Australia
REVIEW RETURNED	09-Jul-2017

GENERAL COMMENTS	The research question is of interest and worthy of studying. The inclusion and exclusion criteria are not clearly defined, and ambiguous. The protocol states people ineligible for revascularisation will be enrolled in the trial. Criteria which make subjects ineligible for revascularisation need to be more clearly defined. The exclusion criteria do not state that people eligible for revascularisation will be excluded. It would be highly unethical to preclude anyone from revascularisation so that they could be in this trial. All outcomes (including safety) need to be defined more precisely (eg ECG criteria for AMI, and "unexpected incidents").

REVIEWER	Yongliang Jia University of Macau, Macau SAR, China
REVIEW RETURNED	10-Jul-2017

GENERAL COMMENTS	1. The manuscript follows the international standard for designing and reporting of randomized controlled trials (CONSORT statement 2010). A new extension of the CONSORT statement was published. I think this manuscript should be checked again according to the extension statement of Chinese herbal medicine. Linde K, Brinkhaus B. Randomized Trials of Chinese Herbal Medicine: A New Extension of the CONSORT Statement. Ann Intern Med. 2017. doi: 10.7326/M17-1067. 2. The discussion of this study should be clearly reported. It seems better to replace some sentences in DISCUSSION to BACKGROUND, for example the first paragraph in DISCUSSION.

	3. There are many grammatical errors throughout the manuscript, such as a kind of Chinese patent medicine in line 42 in Page 2, the patients is treated in line 16 in Page 3. Please improve the language. 4. Please format the References to the guidelines of BMJ Open. References need to be updated. Reference 2 is not appropriate to cite. Reference 23 has missing page.

REVIEWER	Subhuti Dharmananda, Ph.D. Institute for Traditional Medicine and Preventive Health Care Portland, Oregon, USA
REVIEW RETURNED	19-Jul-2017

GENERAL COMMENTS	This study proposal has potential for a useful evaluation of the test medication. However, I believe that in order to reach this potential certain issues must be addressed. Among those mentioned (see attached comments) the most critical is being able to compare the active and control (placebo) groups properly. The issues include age range and anticipated end point event numbers, given how many patients are to be recruited. If this aspect of study design is not improved, I am very concerned that the results will not be a valid and useful indication of the effect of the medicinal formulation. The study group size may seem large (440 for the two groups), but to detect changed risk, the group size is normally much larger. To use the smaller group, one must have very good matching of their characteristics and strong analysis of contributing factors to the observed end point events. 1. Methodology I perceive two methodological problems or potential problems that are related to the primary outcome measurement which is number of cardiovascular incidents during this 24 week observational period. The first problem is the large age range of the study participants, namely 45-75 years. While this large age range makes it easier to recruit the requisite 440 patients for the study, it also makes it much more difficult to compare the treatment groups because of the diversity of patient conditions. The patients in the active and placebo groups are undertaking good preventive health care during the trial, and thus the total number of incidents should be low, meaning that slight variations in the active and placebo study groups can have a large impact on apparent effects of active therapy versus placebo. Therefore, efforts to better match the groups by limiting diversity in age could be important. It is normal and expected that the older patients will experience a higher rate of cardiovascular events, especially in a short observation period, compared to younger patients, and it is likely for older patients to have more contributing factors to cardiovascular events than younger patients. I believe this study would have a much greater potential for useable results if the age range were narrowed to 55-75 years. As an example of rate of events, a recently published study involving people at quite high risk of heart attack and other cardiovascular events (https://www.ncbi.nlm.nih.gov/pubmed/28514624) showed that 12.8% of patients experienced an end-point event over an averaged period of 26 months. Converting to five months, that suggests a rate of about 2.5%.

With 220 patients per group, the total number of patients experiencing end point events would be about 6. The study referenced here involved over 12,000 patients and it was terminated after it was found that the placebo and active groups had the same rates. In another such study, with nearly 5 year follow-up duration, rates of events were also modest and would be difficult to monitor in a small group (this study involved 15,000 (http://www.medscape.org/viewarticle/501390). While these studies not exactly comparable to the proposed one, they illustrate that detection of event rate changes is not an easy task.

The second problem is that cardiovascular events can occur more frequently under certain environmental conditions, for example, extremes of cold or heat. Since some study participants will be involved in some parts of the year and others during other parts of the year, introducing a seasonal variation, and some in the south (e.g. Guangdong) and some in the north (e.g., Beijing), introducing considerable geographic and climatic variation, there will be factors influencing the results that could skew the interpretation of number of events. Cardiovascular events can occur also as a result of a short period of overexertion or after a heavy feast meal, so that the diversity of locations and times of year could contribute in several ways, such as encompassing circumstances that are encountered by some patients and not others. It is a virtual necessity to have several observation and treatment sites and also to provide treatment over the full year, even though an individual's treatment is 24 weeks, so efforts should be made to carefully monitor known contributing factors so that evaluation of results can take them into account.

Therefore, I would strongly recommend a tightening up of the age range for eligibility and an expansion of checks for contributing factors to cardiovascular events.

2. Traditional Chinese Medicine
With regard to the Chinese medicine therapeutics, I have also two major concerns. The first has to do with characterization of the medicine to be applied. The authors have not demonstrated knowledge of the medicinal materials involved. Thus, for example, the patent medicine pill is merely described as a product of Shanghai-Hutchison Pharmaceuticals Limited. Shexiang Baoxin Wan (Wan = Pill) contents may not be fully revealed by the manufacturer. A typical listing of the ingredients are these:

Chinese name	Description	Comments
Chan Su	The venom of a toad, *Bufo bufo*	This agent is known as a cardiotonic, but it can also have cardiotoxicity, depending on dosage; it possesses neurotoxicity.
She Xiang	The gland of the musk deer	The original material is banned from use due to endangered status of musk deer; a synthetic

		compound is used in its place, perhaps muscone.
Niu Huang	The gallstone of ox (water buffalo)	The original material is too rare and costly for use in patent medicines and is substituted by a mixture of some substances intended to have similar effect.
Su He Xiang	An aromatic extract of Liquidambar tree (styrax; storax)	
Rou Gui	Bark of the cinnamon tree	
Bing Pian	Crystalline aromatic component of certain plants, dominated by borneol	Due to high cost, the patent medicine contains synthetic borneol; borneol is known as a cardiac stimulant.
Ren Shen	Root of Chinese ginseng	An extract that includes the ginsensosides specifically

A study such as this should be accompanied by description of the actual contents to the extent possible, so as to allow for comparison with other studies and to attain reproducible results in the follow-up studies. Since the factory is reasonably expected to retain certain proprietary information about this product, certain content specifications may remain undisclosed, such as the proportions of each ingredient. The ingredients list provided is depicted as “chief ingredients,” so there may be others. It is unclear whether this pill is intended for long-term use. Its most common use is for short term applications. The 24 week study period represents a relatively long term and since the implication of a positive result would be that the pill should be taken even longer than 24 weeks to retain lowered risk of cardiovascular events, safety evaluation is critical. In particular, chan su (toad venom) may pose a safety risk (see: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1769273/ and http://opem.or.kr/bbs/board.php?bo_table=m02_13&wr_id=15). However, the main concern to be expressed here is that the content of the pill may have been changing over time, and thus should be characterized for this study.

In terms of prior clinical experience and duration of use, I was surprised to note that a study of this formula for angina pectoris was not referenced (see: https://www.ncbi.nlm.nih.gov/pubmed/9772586). The treatment time in that study was 2 weeks, which is more characteristic of use of this formula. There was also a review of studies of this medicine produced for a forum:

	H. Lin and W. P. Tang, “Systematic Review of Randomized Controlled Trials on treating CHD with Shexiang baoxin wan,” First National Middle-Aged MD Forum Proceedings of Integrative Medicine on Cardiovascular Disease, pp. 147–152, 2008. And, for its use in treating angina: X. G. Zhou, H. W. Wang, and G. B. Yu, “Meta Analysis on treating unstable angina pectoris with Shexiang baoxin wan,” Chinese Traditional Patent Medicine, vol. 26, supplement, pp. 1–6, 2004. Most recently, there was a review and meta-analysis of studies of the formula used in combination with trimetazidine (see: http://en.cnki.com.cn/Article_en/CJFDTotal-PZXX201610004.htm) and as a general adjuvant (see: http://jglobal.jst.go.jp/en/public/20090422/201602200694398355). I think it would be beneficial for the authors of the study proposal to include such references to prior work in order to display similarities and differences in application, dosage, and duration of use between prior work and the current effort. I realize that a discussion of these matters would naturally await the publication of study results, but the authors of the study proposal should take into account prior clinical analysis so that they can seek out and correct methodological flaws, be aware of adverse event profiles, and have a good sense of the time frame for patients experiencing certain therapeutic effects when taking the pills. Thus, for example, some symptoms may be affected promptly, and a data point taken after four weeks would not easily capture that effect. The second concern is that the TCM category of patients to be treated is reported as “deficiency of qi and blood stasis.” Although this formula contains a small amount of ginseng (ren shen), which can serve as a qi tonic for qi deficiency cases, in fact, the absence of supporting herbs for treating qi deficiency demonstrates that this pill is not designed for qi deficiency cases. Rather ren shen can be serving other roles. That the quantity is small is confirmed by the size of the pills and the described nature of the extract. The dominant therapeutic effect of this pill is to treat “phlegm accumulation” or “phlegm mist affecting the orifices of the heart” (another common description is that it “resuscitates” the heart, but that is a secondary effect of dispersing the obstruction). This condition of phlegm obstruction, when translated into modern thinking about cardiovascular disease, can be affiliated with blood stasis, but that is not how the formula was envisioned initially. Rather, the formula design is for the short-term treatment of an obstruction due to phlegm, especially a sudden obstruction, as occurs with angina pectoris or heart attack. The formula contains none of the ingredients commonly applied to blood stasis, such as dan shen, chi shao, mu dan pi, sheng di, chuan xiong, etc. The formula has been depicted elsewhere as regulating the flow of qi, a description that sometimes accompanies aromatics. When using modern TCM categories, ren shen is described as tonifying qi and rou gui as activating yang; in this formula ren shen may be for stabilizing the heart and rou gui for alleviating pain. The point is that using modern TCM therapeutic categories might not fit the original design intention and the selection of qi deficiency and blood stasis patients might not fit the pattern the formula was aimed at. In sum, this formula is inadequately described and may be i

	Incorrectly positioned within the TCM system. Patient selection based on qi deficiency and blood stasis may, in fact, be incorrect. It is true that many cases of CAD fit qi deficiency and blood stasis, but if that is the diagnostic, then another formula would be more suitable. In presenting these concerns, I am suggesting that some more work should be done on the study proposal, and that two changes in the fundamentals of the study proposal be considered: tighten up the age range for participants and reconsider the TCM "zheng" (syndrome) description so that patient selection truly corresponds to formula indications. It does happen in the field of TCM that a formulation that is designed for and initially used for an acute condition (in this case, angina pectoris or heart attack) may find use in a chronic condition (e.g., CAD) perhaps serving to prevent the occurrence of the events for which short-term use has been indicated. The formula might even function by immediately treating the event as it is arising, by virtue of being taken regularly. Therefore, the long term application of the formula may be appropriate. However, if there is a lack of prior clinical experience using the formula this way (24 weeks), extra attention must be paid to potential adverse effects, especially when incorporating potent ingredients, such as toad venom and borneol.

VERSION 1 – AUTHOR RESPONSE

Responses to the comments of reviewer 1
Q1: The inclusion and exclusion criteria are not clearly defined, and ambiguous. The protocol states people ineligible for revascularisation will be enrolled in the trial. Criteria which make subjects ineligible for revascularisation need to be more clearly defined. The exclusion criteria do not state that people eligible for revascularisation will be excluded. It would be highly unethical to preclude anyone from revascularisation so that they could be in this trial.

Response: Thank you for your suggestions. All of the questions raised were so important for us to improve the quality of the paper.
First, the question is "the inclusion and exclusion criteria are not clearly defined, and ambiguous. The protocol states people ineligible for revascularisation will be enrolled in the trial." On this issue, we have conducted in-depth discussion. However, there are few consensus on the definition of CAD not amenable to revascularization. Referring to some Chinese expert opinions and a few literature reports, we summed up that CAD not amenable to revascularization mainly referred to severe diffuse left main coronary artery and three-vessel stenosis, calcification or lesions or CAD complicated with severe multiple-organ disease, such as severe heart failure, infection, blood diseases, cancer cachexia, lung dysfunction or renal insufficiency. (C. Mannheimer, P. Camici, M. R. Chester, et al. The problem of chronic refractory angina Report from the ESC Joint Study Group on the Treatment of Refractory Angina. Eur Heart J 2002 ;(23):355-370.) Patients who can't undergo PCI or CABG are very common in our clinic, and they have no options but take conservative treatment. In clinical practice, we found that for these patients, the combination of Chinese and Western medicine treatment could often relieve symptoms and improve the prognosis. So we take these patients as the objects of our study and choose the Shexiang Baoxin pill to treat CAD which belong to Qi deficiency and blood stasis syndrom. Before the patient is selected, both cardiologists and cardiac surgeons will decide whether the CAD patients can carry out revascularization.

The patients that are eligible for revascularization will be excluded. In order to further refine this definition, we are currently conducting an expert questionnaire survey, hoping to define the definition of the disease as soon as possible. And we have added one exclusion criteria in page 10. It was revised as below.
“g) patients who are eligible for revascularization.” (P 6)

Q2: All outcomes (including safety) need to be defined more precisely (eg ECG criteria for AMI, and "unexpected incidents").

Response: Thank you for your suggestions. I have defined the outcomes more precisely. It’s revised as below.
“The primary outcomes include mortality and major adverse cardiovascular events (including angina, acute myocardial infarction, pulmonary embolism and aortic dissection)”; (P 9) “electrocardiogram (abnormal ST-T changes) ”(P 9)

Responses to the comments of reviewer 2
Q1: The manuscript follows the international standard for designing and reporting of randomized controlled trials (CONSORT statement 2010). A new extension of the CONSORT statement was published. I think this manuscript should be checked again according to the extension statement of Chinese herbal medicine. Linde K, Brinkhaus B. Randomized Trials of Chinese Herbal Medicine: A New Extension of the CONSORT Statement. Ann Intern Med. 2017. doi: 10.7326/M17-1067.

Response: Thank you for your suggestions. We have referenced the new extension of the CONSORT statement (in page 13) and revised the manuscript according to the Spirit 2013 Statement and the extension statement of Chinese herbal medicine. And we have completed and uploaded the two checklists.

Q2: The discussion of this study should be clearly reported. It seems better to replace some sentences in DISCUSSION to BACKGROUND, for example the first paragraph in DISCUSSION.

Response: Thank you for your suggestions. We have replaced the first paragraph in DISCUSSION to BACKGROUND. It has been revised as below.
“However, in a contemporary series of patients undergoing coronary angiography, 28.8% of patients had significant CAD and did not undergo complete revascularization, among which 12.8% was partially revascularized, 9.3% was managed medically and 6.7% had "no-options"; these patients exhibited higher mortality at 3 years compared with completely revascularized patients”. (P3)

Q3: There are many grammatical errors throughout the manuscript, such as a kind of Chinese patent medicine in line 42 in Page 2, the patients is treated in line 16 in Page 3. Please improve the language.

Response: Thank you for your suggestions. We have revised this paper under the help of American Journal Experts. The modified part of the paper is marked as red colour. The “a kind of Chinese patent medicine” in line 42 in Page 2 was revised as “type of Chinese patent medicine” in Page 1. And we have deleted “the patients is treated”.

Q4: Please format the References to the guidelines of BMJ Open. References need to be updated. Reference 2 is not appropriate to cite. Reference 23 has missing page.

Response: Thank you for your suggestions. We have rormatted the Reference to the guidelines of BMJ Open. Reference 2 in the original manuscript has been replaced by the new reference 2 (C. Mannheimer, P. Camici, M. R. Chester, et al. The problem of chronic refractory angina Report from the ESC Joint Study Group on the Treatment of Refractory Angina. Eur Heart J 2002 ;(23):355-370). The reference 23 is from page 675 to page 690.

Responses to the comments of reviewer 3
Q: This study proposal has potential for a useful evaluation of the test medication. However, I believe that in order to reach this potential certain issues must be addressed. Among those mentioned (see attached comments) the most critical is being able to compare the active and control (placebo) groups properly. The issues include age range and anticipated end point event numbers, given how many patients are to be recruited. If this aspect of study design is not improved, I am very concerned that the results will not be a valid and useful indication of the effect of the medicinal formulation. The study group size may seem large (440 for the two groups), but to detect changed risk, the group size is normally much larger. To use the smaller group, one must have very good matching of their characteristics and strong analysis of contributing factors to the observed end point events.

Response: Thank you for your suggestions. All of the questions raised were so important for us to improve the quality of the paper.

Q1: The problem is “the large age range of the study participants, namely 45-75 years”.

Response: Thank you for your suggestions. In the paper, I have revised the age range as 55-75 years in Inclusion criteria in page 6.

Q2: The problem is “cardiovascular events can occur more frequently under certain environmental conditions, so efforts should be made to carefully monitor known contributing factors so that evaluation of results can take them into account.”

Response: Thank you for your suggestions. In our study, we took a multi-center treatment which was conducive to observe the geographical effect on the treatment. However, due to the time constraints and funding constraints, we set the treatment cycle for 24 weeks. It is not conducive to observing the effect of the season on the patient's medication effect. Therefore, we’ll record each patient's entry time carefully. It may be helpful for later results analysis.

Q3: The problem is “the authors have not demonstrated knowledge of the medicinal materials involved.”

Response: Thank you for your suggestions. We have added a form to the paper which describes the composition and characteristics of Shexiang Baoxin pill. (P 7 P8)

Q4: The problem is “it is unclear whether this pill is intended for long-term use.” Response: Thank you for your suggestions. Experimental studies have shown that SBP is quickly absorbed in the body, is quickly eliminated and has a short duration of action. Although toad venom is toxic when administered alone, its toxicity may be reduced by extending the peak time of toad steroid ingredients via other compatible ingredients in the SBP, thus showing the scientific nature of compound compatibility. Besides, previous studies have shown that long-term SBP administration could reduce the occurrence of angina pectoris events and several other clinical events and reduce the dosage of nitrates used in patients with stable angina pectoris. In addition, the adverse reactions to the SBP are mild, and studies have not shown that the SBP is harmful to liver or kidney function [15-19] .

Q5: Thank you for your suggestions. The question is “this formula is inadequately described and may be incorrectly positioned within the TCM system”.

Response: Syndrom of “phlegm mist affecting the orifices of the heart” often occurs in patients with acute attack of angina pectoris. The musk, borneol, toad and storax contained in the SBP have the effect of activating qi and inducing resuscitation. Therefore, the SBP can be used in the treatment of acute attacks of angina pectoris.
However, CHD occurs more frequently in the elderly whose Yang Qi is originally deficient. Qi deficiency can lead to blood stasis, and then form the syndrome of qi deficiency and blood stasis syndrom. The SBP contains 27% of the ginseng extract, 24% of the cinnamon, 6% of the musk, 4% of the bezoar, 16% of the fleshy bacon, 4% of the toad and 19% of the borneol. (Song H. Pharmacology studies and evaluation of clinical application on Shexiang Baoxin pills. Chinese Traditional Patent Medicine 2002;2:131-133. Chinese) Ginseng extract and cinnamon have the function of nourishing qi warming yang. Qi is the commander of blood and Qi flow promotes blood transportation, so the SBP have the function of supplementing Qi and promoting blood circulation. Therefore, it’s suitable for CHD patients who manifest Qi deficiency and blood stasis syndrome.
Besides, Clinical studies have shown that CHD patients who manifest Qi deficiency and blood stasis syndrom or Qi stagnation and blood stasis syndrome can greatly benefit from long-term SBP administration. Therefore, we adopted SBP to treat CHD patients with Qi deficiency and blood stasis syndrome.

In conclusion, we have learned so much through revising this article again under the guidance of the editor’s kind help and suggestions. I am looking forward to get further guidance from you. Thank you very much.

VERSION 2 – REVIEW

REVIEWER	Subhuti Dharmananda, Ph.D. Institute for Traditional Medicine (ITM) USA
REVIEW RETURNED	25-Sep-2017

GENERAL COMMENTS	I congratulate the authors on their revision. I have expressed in the additional information provided here a minor concern for depicting TCM as "alternative and complementary medicine" with which you may or may not agree, and expanded my stated concern about sample size with recommendations for changing the manuscript but keeping the sample size as proposed. The revised manuscript for bmjopen-2017-018052.R1 is very much improved over the original submission. The introductory and explanatory aspects of this manuscript are clearer, more complete, and provide a better depiction of the study background and plan. Based on those improvements, I am going to approve the study proposal, but wish to point out one terminology aspect I would prefer to see changed and would like to reiterate one study design aspect that is not changed and that remains problematic; I do not expect this to be changed, but the consideration should be elaborated further in the last section of the manuscript. While the manuscript has some errors in sentence structure and spelling, I would like to recommend a change in the way traditional Chinese medicine is being characterized. There are two manuscript references to the subject where I’d make the change:

	1. Delete the phrase in the background section set off by commas: “a popular type of complementary and alternative medicine,” as description of Chinese herbal medicine. This description unnecessarily downplays the historical development and widespread modern use of Chinese medicine, with considerable incorporation of TCM into the total medical system of China. TCM has a theoretical basis rooted in the long tradition, and is accompanied by research such as provided for in the manuscript. In particular, Chinese medicine should not be viewed as alternative medicine, and by depicting it as popular, this sets it far apart from revascularization therapy, which would hardly be described as “popular” even if it is the most valued treatment for CAD. Alternative medicine characteristically has little or no theoretical or historical background, but stands opposed to modern medicine and offers a treatment that is alternative to it. As in this paper, Chinese medicine is being used in the setting of modern medicine and it is being suggested to be used in certain cases where modern medicine does not currently have a suitable offering, so this is not an alternative but a potentially valuable treatment in itself. And, although the designation “complementary” serves better to depict the current role of Chinese medicine, in which it is usually employed along with modern medicine to “complement” it, the term complementary medicine fails to distinguish between medical systems with a rich historical basis, such as TCM, and something that has been devised recently. It is better to stick to the overall description that follows this introductory sentence. The designation “alternative and complementary” is “popular” these days, but it is actually not a good terminology for TCM. 2. Likewise, later in the paper in the discussion section, it is stated that: “As an alternative and complementary medicine, Chinese herbal medicine is attracting attention.” Chinese medicine can attract attention as a valid medicine in itself, not just as another example of alternative and complementary medicine. It can be said that “Chinese herbal medicine has been attracting attention by virtue of its extensive use in China and the growing body of research pointing to its effectiveness.” (or something along these lines) One wording error I believe is present which would not be found in correcting misspelling, is this statement in the discussion section: “large-sample, retrospective, randomized controlled studies are scarce.36 I believe the intended sentence would have the term prospective in place of retrospective. Retrospective studies are not randomized. The study described in this manuscript is prospective. In my review of the prior manuscript I objected that the number of patients and duration of study would be insufficient to provide significant data with regard to adverse events (that is, cardiovascular events intended to be prevented by the pills). I do not expect this aspect of the study to be changed and acknowledge that in keeping with my recommendation the age range was properly tightened up. The justification for the number of patients that has been given in the manuscript under the heading sample size is: “The sample size was calculated using the concept of efficiency as presented by Xie.25” No other references are given in the paragraph elaborating this initial statement. Reference 25 is not to a methodology paper, as one would expect, with a presented concept of efficiency pointing to calculations for number of patients and duration of study, but it refers instead to a small study published in 2014.

	The study abstract, which I was easily able to access: (https://caod.oriprobe.com/articles/45070653/Heart_of_Musk_Pill_Combined_Western_Medicine_Therapy_of_Coronary_Heart.htm), displays some of the poorest of methodological approaches that have been used in China. The article was but two pages long (in Chinese characters; may translate in English to almost three pages). The abstract gave cure rates, effective rates, and no effect rates, involved randomization by the "coin flip method" and had a treatment group size (50 control, 50 treatment) and duration (two months) that was also too short for the intended purpose. Therefore, I am disappointed in the basis that was selected for determining the group size in the present study. I would hope that the authors could find another justification or leave out this part, stating, rather, that the group size is determined by comparison with other TCM treatments for coronary artery disease and perhaps add a couple more references of studies to show examples. The last paragraph of the current manuscript states (in full): "There are also some limitations in this study that should be considered. Due to the restriction of research project funds and trial period, the treatment duration will be short, and thus, additional RCTs with long-term follow-up are warranted to determine the efficacy and safety of the SBP." I believe a better statement would be: "A limitation in this study is the number of patients (440) and duration of treatment (24 weeks) that can be arranged even after incorporating seven treatment facilities in the process of recruitment, treatment, and observation. This limitation is primarily associated with the relative infrequency of CAD that is not amenable to revascularization and the strict requirements for patient participation, randomization, and observation over six months. As a result, the comparison between control group and SBP treatment group primary outcome, that is, the number of adverse cardiovascular events for each group, may be difficult to distinguish even with an effective therapy. That is because the total number of events for each group can be relatively small, and the total number of events will be dependent on the severity of CAD in the recruited population. However, for the accompanying measures, the secondary outcomes for this study, such as C-reactive protein, B-type natriuretic peptide, and electrocardiogram, which together help reveal patient cardiac physiological status and risk factors for such adverse events, the group size and duration will be adequate to reveal any significant differences between the control and treatment groups. If positive findings in primary and secondary outcomes are found, additional RCTs with long-term follow-up are then warranted to determine the efficacy and safety of the SBP." By so stating, if it turns out that the number of adverse events is relatively small and if the differences are not major, an explanation (that is correct, and not simply a means to dismiss the results) has been provided already. Should it happen that there are relatively large numbers of events, there is also an explanation (that is correct), namely that the population recruited had an overall large proportion of severe cases yielding adverse event observations within six months. With regard to other measures, such as C-reactive protein which is a measurable number for each patient, the number of patients is, indeed, adequate, because, it can be shown, the range of variation in the likely study population and range of measurement error is small enough that in a population of 220

	(perhaps more like 190 completing the study), the statistically averaged figures will be significant and differences can be significant). This difference between reliability of adverse event numbers and test measurements is because these changes can precede events and have a range other than 0 (no event) or 1 (event). For example, with C-reactive protein, supposing the SBP reduces the measurement, this illustrates a lowering of known risk factor, but in the 24 weeks duration, that change might not show up in a change in "events" (or only a very small change in a small number of events). Thus, even though one would like to show that SBP is saving lives (either from death or from debility and hospitalization) by preventing these adverse events, that might not be possible (in fact, is probably not possible to show definitively), but it should be possible to show changes in these measures of cardiovascular status and risk of adverse events. I do not believe that funding limitations should be cited as a reason for the study size and duration limitation. While, in fact, funding may not permit a larger study at this time, a lack of funds can justify not carrying out the study at all, rather than proceeding with an inadequate study. In fact, to make a larger scale study is a very substantial undertaking, as will be noted by U.S. studies involving thousands of patients with treatment times over a year or longer. Arranging such a large study not only requires more funds, but also a big commitment to this project at all the facilities that would be willing to participate. Should this study point to the effectiveness of SBP with obvious clinical significance, then a larger study would gain support. Also, it is very difficult to enroll patients in a study that persists for more than 24 weeks because of compliance issues; typically, patient situations change over time. To pursue a study like this long term, it is important that the physicians managing the patients are convinced that this treatment method has a good chance of becoming standard.

VERSION 2 – AUTHOR RESPONSE

Responses to the comments of reviewer 3
Q: The problem is the concern for depicting TCM as "alternative and complementary medicine" and about sample size with recommendations for changing the manuscript but keeping the sample size as proposed.

Response: Thank you for your suggestions. All of the questions raised were so important for us to improve the quality of the paper. Firstly, traditional Chinese medicine is an important part of complementary and alternative medicine. TCM plays an important role in Chinese medical system. The purpose of our study is to evaluate the therapeutic effect of TCM objectively. If positive findings are identified, the beneficial effect of TCM for CAD not amenable to revascularization will be verified. Otherwise, if negative findings are identified, the genuine effect of TCM for CAD not amenable to revascularization will also be verified. In summary, objective evaluation of the efficacy of TCM is the main purpose of our study. Secondly, due to the limitation of funds, we are not able to increase the sample size. Besides, the previous large-scale studies on the end points of CAD are exactly not the same as our study. The condition of patients with angina pectoris is relatively mild, which is conducive to a large sample of clinical research. Patients in our study have the characteristic of severe condition, poor prognosis, more complications and high mortality. If we can get some results from 440 subjects, it will be a good attempt. Thirdly, to observe the end points, one-year follow-up period may not be enough. So we decide to extend the follow-up period to 5 years after our discussion.

VERSION 3 – REVIEW

REVIEWER	Subhuti Dharmananda, Ph.D. Institute for Traditional Medicine and Preventive Health Care, USA
REVIEW RETURNED	29-Nov-2017

GENERAL COMMENTS	The proposed study protocol is acceptable. Please note that there are some simple spelling errors occasionally present. I had raised some concerns in my last review and the authors felt that there was not a need to make changes based on those comments; this is acceptable.