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)	Chinese Herbal Medicine for Patients with Vascular Cognitive Impairment No Dementia: Protocol for A Systematic Review
AUTHORS	Feng, Mei; Lu, Jingmin; May, Brian H.; Liu, Shaonan; Guo, Xinfeng; Zhang, Anthony; Xue, Charlie; Lu, Chuan-jian

VERSION 1 - REVIEW

REVIEWER	Wu Taixiang Chinese Clinical Trial Registry, West China Hospital, Sichuan University
REVIEW RETURNED	29-Oct-2015

GENERAL COMMENTS	You said you will include randomised controlled trial only. Please specify for those publications in which “randomly allocated patients” was mentioned, but there was no any information of randomisation procedure, or how to generate a random number sequence, or how to conduct allocation concealment, how do you do then? How do you make sure such a study was real randomised controlled trial?

REVIEWER	Hongcai Shang Beijing university of Chinese medicine, China
REVIEW RETURNED	11-Nov-2015

GENERAL COMMENTS	This manuscript is very interesting and valuable for clinicians; It's according to PRISMA checklist.

REVIEWER	Jagan Pillai Cleveland Clinic
REVIEW RETURNED	27-Nov-2015

GENERAL COMMENTS	The authors present a protocol for a systematic review of published studies to analyze the efficacy of Chinese Herbal medicine on Vascular cognitive impairment no dementia (VCInD). This is worthy of study but as this is a specialized intervention more likely to be performed in China and as the authors note VCInD is difficult to characterize it might be useful to report on some additional variables of interest while reporting effect sizes to a general audience. 1. What are the risk vascular risk factors quantified in each study and how well were the controlled during the duration of the study (HbA1c, Blood Pressure, Lipids) 2. Are the results controlled for age, education and number and

	severity medical comorbidities 3. How many of the studies were performed among Chinese subjects alone and among them how many of these studies were RCTS 4. In addition, report each type of CHM intervention and their effects separately

REVIEWER	Francesco Panza, MD, PhD Neurodegenerative Disease Unit, Department of Basic Medicine, Neuroscience, and Sense Organs, University of Bari Aldo Moro, Bari, Italy
REVIEW RETURNED	14-Dec-2015

GENERAL COMMENTS	Feng and colleagues described the design and the protocol for a systematic review on the efficacy and safety of Chinese herbal medicine (CHM) for the treatment of patients with vascular cognitive impairment but no dementia (VCIND). Some minor points to clarify: 1. Proposed Methods and Analysis have been described in details and appeared to be methodologically sound, but in the Introduction section the Authors should give more details on the available meta-analytic evidence on this issue (references 12 and 13 in the present manuscript). 2. Discussion section: some meta-analytical evidence and possible mechanisms of action of CHM on VCIND should be described, at least for Gingko biloba (please, consider to include: Cochrane Database Syst Rev 2007 Apr 18; (2):CD003120 and J Alzheimers Dis. 2015;43(2):605-11) and huperzine A. 3. Discussion section: please, consider to include a study limitations section.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
Taixiang Wu
Chinese Clinical Trial Registry, West China Hospital, Sichuan University
Comment：
You said you will include randomised controlled trial only. Please specify for those publications in which “randomly allocated patients” was mentioned, but there was no any information of randomisation procedure, or how to generate a random number sequence, or how to conduct allocation concealment, how do you do then? How do you make sure such a study was real randomised controlled trial?
Response: Thank you for your comments. Randomization plays a fundamental role in balancing prognostic factors, on average, evenly across intervention groups of randomized controlled trial.1 A true random allocation can reduce the selective bias and increase the authenticity and reliability of research results. But some trials, although reported as RCTs, lacked an adequate description of the procedure of randomization sequence generation and allocation concealment.2 So our team will make efforts as follows:
1. As previously described, we have included the domains of randomization sequence generation and allocation concealment in the risk of bias assessment. The decisions will be justified according to the criteria described in the Cochrane Handbook 5.1.
2. In addition, we will retrieve the related protocol in clinical trials registration websites. If the relevant

details of these two domains are unclear we will contact the first author/s or corresponding author/s through E-mail or telephone for clarification.
3. We also plan to do sensitivity analyses according to the classifications of risks in randomization sequence generation and allocation concealment to investigate the robustness of the study results.
Action: The revisions are seen in the text of clean version (page 6, line 156-160 and page 7, line 185-187).

Reviewer 2:
Hongcai Shang
Beijing university of Chinese medicine, China
Comment：This manuscript is very interesting and valuable for clinicians; it's according to PRISMA checklist.
Response: Thank you for your comments.

Reviewer 3:
Jagan Pillai
Cleveland Clinic

The authors present a protocol for a systematic review of published studies to analyze the efficacy of Chinese Herbal medicine on Vascular cognitive impairment no dementia (VCIND).
This is worthy of study but as this is a specialized intervention more likely to be performed in China and as the authors note VCIND is difficult to characterize it might be useful to report on some additional variables of interest while reporting effect sizes to a general audience.
Comment 1~2：
1. What are the risk vascular risk factors quantified in each study and how well were the controlled during the duration of the study (HbA1c, Blood Pressure, Lipids)?
2. Are the results controlled for age, education and number and severity medical comorbidities?
Response: Thank you for your suggestion. Vascular risk factors play an important role in the pathogenesis of VCIND. Furthermore, vascular risk factors are treatable, so it should be possible to prevent, postpone, or mitigate VCI.3 Quantification of vascular risk factors is necessary not only in diagnosis, but also in outcome assessment. As there is a lack of internationally recognized diagnostic criteria for VCIND, it is difficult to identify whether the cognitive function impairment was caused by vascular risk factors. After re¬ferring and summarizing several diagnostic criteria used in international clinical trials4 5 6 and Chinese expert consensus7 8 9, we revised the inclusion criterion to define the relationship between vascular risk factors and VCIND. (page 4, line 93-96).
At the same time, it is necessary to extract detailed data on demographic characteristics and vascular risk factors in VCIND. So we have re-written this part according to the reviewer's comments. First, we will add some extraction variables about demographic characteristics (e.g. age, sex, duration, education level, life styles (e.g. smoking, alcohol consumption); Second, we will add baseline data collection which are related to VCIND, such as vascular risk factors (e.g. hypertension, hyperlipidemia, diabetes), severity of medical comorbidities and current use of medications (e.g. anti-platelet aggregation drugs, anti-hypertension drug, hypoglycemic drugs) 10 11; Third, we will perform subgroup analysis according to the different demographic characteristics or vascular risk factors, if possible. If necessary, Meta regression will be performed to control the variable of age, education, number, severity medical comorbidities and vascular risk factors etc.
Action: We have rephrased the section (page 5, line 138-142； page 6, line 179-181).
3. How many of the studies were performed among Chinese subjects alone and among them how many of these studies were RCTS?
Response: Currently we have completed the preliminary search and 1445 records are identified through the databases and other sources. More than 20 RCT studies meet the inclusion criteria, but the exact number needs to be rechecked and updated because the screening and double checking is ongoing.

4. In addition, report each type of CHM intervention and their effects separately.
Response: We agree with the reviewer's suggestion and add subgroup analysis according to different route of administration, dosage, preparations of CHM interventions (page 7, line 182-183).

Reviewer: 4
Francesco Panza, MD, PhD
Neurodegenerative Disease Unit, Department of Basic Medicine, Neuroscience, and Sense Organs, University of Bari Aldo Moro, Bari, Italy

1. Proposed Methods and Analysis have been described in details and appeared to be methodologically sound, but in the Introduction section the Authors should give more details on the available meta-analytic evidence on this issue (references 12 and 13 in the present manuscript).
Response: Thank you for your suggestion. We have given more details on the meta-analytic evidence of CHM for VCIND (page 3, line 68-76).

2. Discussion section: some meta-analytical evidence and possible mechanisms of action of CHM on VCIND should be described, at least for Gingko biloba (please, consider to include: Cochrane Database Syst Rev 2007 Apr 18; (2):CD003120 and J Alzheimers Dis. 2015;43(2):605-11) and huperzine A.
Response: We have added the meta-analytical evidence and possible mechanism of action about Gingko biloba extract EGb 761 and Huperzine A (page 7, line 204-215).

3. Discussion section: please, consider to include a study limitations section.
Response: We have added a limitations section in the article (page 8, line 221-225).

Other changes:
1. Some editorial errors such as spelling and grammar have been revised.
2. We have revised and formatted the manuscript text and reference list according to the comments and format of BMJ OPEN.
3. Search strategy used in PubMed database has been presented at table 2 in the manuscription. In addition, we have attached appendix 1 to show the detail steps of search strategy in PubMed database.
4. We have filled in a PRISMA-P check-list and please find the attached appendix 2.

END

Reference:
1. Julian PT Higgins, Sally Green. Cochrane handbook for systematic review of intervention version 5.1.0 (updated March 2011). The Cochrane Collaboration 2011. http://www.cochrane-handbook.org (accessed Jun 2015): page 8.27.
2. Wu TX, Li YP, Bian ZX, et al. Randomized trials published in some Chinese journals: how many are randomized?, Trials 2009; 10:46.
3. Hachinski V, Iadecola C, Petersen RC, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke 2006; 37:2220–41.
4. Ingles JL, Wentzel C, Fisk JD, et al. Neuropsychological predictors of incident dementia in patients with vascular cognitive impairment, without dementia. Stroke 2002; 33: 1999–2002.
5. Wentzel C, Darvesh S, MacKnight C, et al. Inter-rater reliability of the diagnosis of vascular cognitive impairment at a memory clinic. Neuroepidemiology 2000; 19: 186–93.
6. Neuropathology Group. Medical Research Council Cognitive Function and Aging Study. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Lancet. 2001; 357:169-75.
7. Experts consensus group of Chinese prevention and treatment of cognitive dysfunction. Experts'

common understanding of Chinese prevention and treatment of cognitive dysfunction. Chin J Intern Med 2006; 45:171–73.
8. Experts consensus group of Vascular cognitive impairment. Experts' common understanding of vascular cognitive impairment. Chin J Intern Med 2007; 46:1052–55.
9. Jia JP. Attention to early diagnosis and intervention of vascular cognitive impairment. Chin J Neurol 2005; 38:4–6.
10. Wang R, Fratiglioni L, Laukka EJ, et al. Effects of vascular risk factors and APOE ε4 on white matter integrity and cognitive decline. Neurology 2015;84:1128-35.
11. Raj N Kalaria, Gladys E Maestre, Raul Arizaga, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. Lancet Neurol 2008; 7: 812–26.

VERSION 2 – REVIEW

REVIEWER	Taixiang Wu Chinese Clinical Trial Registry West China Hospital, Sichuan University
REVIEW RETURNED	15-Feb-2016

GENERAL COMMENTS	1. The concept of "Types of Interventions" itself includes comparators. So, the "Types of comparators" should be combined with Types of Interventions" together. 2. "Primary outcomes" and "Secondary outcomes" should be put together under a headline "Types of outcome measures".

REVIEWER	Francesco Panza, MD, PhD Neurodegenerative Disease Unit, Department of Basic Medicine, Neuroscience, and Sense Organs, University of Bari Aldo Moro, Bari, Italy
REVIEW RETURNED	09-Feb-2016

GENERAL COMMENTS	All my previous concerns have been satisfactorily addressed.