

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)	Efficacy, Safety and Response Predictors of Adjuvant Astragalus for Diabetic Kidney Disease (READY) – Study Protocol of an Add-on, Assessor-blind, Parallel, Pragmatic Randomised Controlled Trial
AUTHORS	CHAN, Kam Wa; KWONG, Alfred; TSUI, Pun Nang; CHEUNG, Simon Chi Yuen; CHAN, Gary; CHOI, Wing Fai; YIU, Wai Han; ZHANG, Yanbo; Wong, Michelle Man-Ying; Zhang, Zhang-Jin; TAN, Kathryn; Lao, Lixing; TANG, Sydney

VERSION 1 – REVIEW

REVIEWER	Susumu Ogawa Institute for Excellence in Higher Education, Division of Research in Student Support, Section of Clinical Medicine, Tohoku University, Sendai, Japan.
REVIEW RETURNED	06-Aug-2020

GENERAL COMMENTS	<p>The authors try to evaluate the effectiveness of add-on astragalus on type 2 diabetic patients with stage 2 to 3 chronic kidney disease and macroalbuminuria and identify related response predictors. Then, they planned randomized clinical trial that used astragalus.</p> <p>#1. It is necessary to add a pharmacologic explanation concerning astragalus to Introduction section. Why is it effective on DKD? It is necessary to explain the reason why you paid attention to this herb from the elements of this herb and the pathology of DKD.</p> <p>#2. Sample size is small as the research of this type. In this sample size, the reliability of research results becomes small though power analysis is presented.</p> <p>#3. It is necessary to present the allocation factor at the randomization.</p> <p>#4. To exclude the influence of the intake of water, it is necessary to do the drinking water of same doses to control subject.</p> <p>#5. Please present set grounds whose examination period is 48 weeks.</p> <p>#6. Is there payment of the remuneration to the participant in this research?</p> <p>#7. It seems that urinary albumin excretions change extremely easily and the change in eGFR is small in 48-week. These evaluations will annoy you in the future.</p>
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REVIEWER	Dr. Delia Timofte, MD, PhD Emergency University Hospital Bucharest - Department of Hemodialysis , Romania
REVIEW RETURNED	14-Sep-2020

GENERAL COMMENTS	The manuscript is very interesting, well-organized and structured, with all the necessary sections.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

#1. It is necessary to add a pharmacologic explanation concerning astragalus to Introduction section. Why is it effective on DKD? It is necessary to explain the reason why you paid attention to this herb from the elements of this herb and the pathology of DKD.

As explained in the Introduction section, the active ingredient of astragalus (astragaloside IV) has been shown to ameliorate podocyte apoptosis, foot process effacement, mesangial expansion, glomerulosclerosis and interstitial fibrosis through regulating the NF- κ B and TGF- β 1 signalling pathway, which partly explained the renoprotective effect. Systematic reviews showed that astragalus could enhance creatinine clearance, reduce albuminuria and reduce blood pressure among CKD and DKD patients. Meta-analyses also showed that astragalus' effect in improving renal clearance and reducing albuminuria was better than routine care (without ACEI or ARB) and the efficacy was comparable to ACEI or ARB. We decided to use astragalus as the intervention also because it is the most frequently used CM or dietary herb for DKD. Additional description of the pathology of DKD has been added to the Introduction section.

#2. Sample size is small as the research of this type. In this sample size, the reliability of research results becomes small though power analysis is presented.

As explained in the sample size calculation, the primary objective of this trial is to evaluate key clinical outcomes and to perform a preliminary analysis on potential response predictors, we calculated the sample size based on the control of inflation factor (IF) to the estimation of sample size for the subsequent large-scale studies. Further large-scale implementation studies will able the evaluation of real-world effect in practice.

#3. It is necessary to present the allocation factor at the randomization.

The allocation factor has been added to the Recruitment and Randomisation section.

#4. To exclude the influence of the intake of water, it is necessary to do the drinking water of same doses to control subject.

Since this trial is positioned to be a pragmatic trial, we believe the use of standard care with no further intervention would best reflect the real-world practice and the future application scenario of this trial.

(1) Relevant explanation has been added to the Intervention and Control section.

#5. Please present set grounds whose examination period is 48 weeks.

The primary outcome is the change of glomerular filtration rate (GFR). (2) We believe reporting 1-year (48-week) change would be necessary to avoid extrapolation of the GFR slope as the progression of disease takes years. Study duration of over 48 weeks may lead to substantial increase in attrition and is limited by resources as an investigator-initiated study. Justification has been added to the Outcome Measurement section.

#6. Is there payment of the remuneration to the participant in this research?

We provide travel allowance to the patient with no further reimbursement.

#7. It seems that urinary albumin excretions change extremely easily and the change in eGFR is small in 48-week. These evaluations will annoy you in the future.

Thank you for the kind reminder.

Reviewer: 2

The manuscript is very interesting, well-organized and structured, with all the necessary sections.

Thank you.

VERSION 2 – REVIEW

REVIEWER	Susumu Ogawa Institute for Excellence in Higher Education, Division of Research in Student Support, Section of Clinical Medicine, Tohoku University, Japan.
REVIEW RETURNED	08-Dec-2020
GENERAL COMMENTS	The authors carefully corrected the manuscript according to my comments.