ABSTRACT

Introduction Diabetic kidney disease (DKD) is a prevalent and costly complication of diabetes with limited therapeutic options, being the leading cause of end-stage kidney disease in most developed regions. Recent big data studies showed that add-on Chinese medicine (CM) led to a reduced risk of end-stage kidney disease and mortality among patients with chronic kidney disease (CKD) and diabetes. Astragalus, commonly known as huang-qí, is the most prescribed CM or used dietary herb in China for diabetes and DKD. In vivo and in vitro studies showed that astragalus ameliorated podocyte apoptosis, foot process effacement, mesangial expansion, glomerulosclerosis and interstitial fibrosis. Nevertheless, the clinical effect of astragalus remains uncharacterised. This pragmatic clinical trial aims to evaluate the effectiveness of add-on astragalus in patients with type 2 diabetes, stage 2–3 CKD and macroalbuminuria, and to identify related response predictors.

Methods and analysis This is an add-on, assessor-blind, parallel, pragmatic randomised controlled clinical trial. 118 patients diagnosed with DKD will be recruited and randomised 1:1 to receive 48 weeks of add-on astragalus or standard medical care. Secondary endpoints are the changes in estimated glomerular filtration rate and urine albumin-to-creatinine ratio between baseline and treatment endpoint. Secondary endpoints include adverse events, fasting blood glucose, glycated haemoglobin, lipids and other biomarkers. Adverse events are monitored through self-complete questionnaire and clinical visits. Outcomes will be analysed by regression models. Subgroup and sensitivity analyses will be conducted for different epidemiological subgroups and statistical analyses. Enrolment started in July 2018.

Ethics and dissemination This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West/East/Kowloon Central clusters (UW 16-553/HKEC-2019-026/REC (KC/KE)-19-0049/ER-4). We will report the findings in medical journals and conferences. The dataset will be available on reasonable request.

Strengthen and limitations of this study

► Existing epidemiological data suggested that Chinese medicine (CM) was associated with retarded progression of renal function among diabetic kidney disease (DKD) patients. It is timely to perform a clinical trial on astragalus, the most used herbs in diabetes and DKD with unclear clinical effectiveness.

► The inclusion/exclusion criteria, primary outcome measurement and the corresponding analyses are designed according to conventionally used parameters to facilitate further meta-analysis with other clinical studies for a wide range of audience.

► A responder analysis is built into the trial as the secondary analysis to identify possible factors (including biomarkers and symptom-based diagnosis) that could lead to more personalised the use of astragalus.

► As the trial is open-label, subjective outcomes including quality of life could not be assessed.

INTRODUCTION

In 2019, it was estimated that 463 million (9.3%) people were living with diabetes worldwide and the figure was projected to reach 578 million by 2030, with the highest prevalence in North America at present.1 In 2017, the healthcare expenditure on diabetes reached US$850 billion globally (11.6% of global health expenditure).2,3 Diabetic
kidney disease (DKD) refers to the chronic kidney disease (CKD) caused by long-standing diabetes. DKD presents in more than one third of all diabetic patients and is the leading cause of end-stage kidney disease in many developed regions which requires replacement therapy in the form of dialysis and transplantation. In Hong Kong, the incidence of diabetes-related end-stage kidney disease increased from 26.2% in 1996 to 49.6% in 2013 and end-stage kidney disease increased 5.22 times the annual direct medical cost to the local public health system. Furthermore, DKD was accounted for 23.4% (31.1% vs 7.7%) and 16 years shorter life expectancy in Taiwan when compared with those without diabetes and kidney diseases.

The risk factors and pathogenesis of DKD are heterogeneous involving metabolic, inflammatory, haemodynamic, and many other pathways. Thinning of glomerular basement membrane, mesangial expansion, effacement of foot process, formation of Kimmelstiel-Wilson nodules, glomerulosclerosis and interstitial fibrosis are the classical histopathological features of diabetic nephropathy. Conventional blockade on the renin-angiotensin-aldosterone system (RAAS) offers limited effect on clinical outcomes. In a previous meta-analysis of 9797 patients with stage 3–5 CKD, RAAS blockade did not reduce all-cause mortality and only provided a mild risk reduction in the composite endpoint of replacement therapy initiation or doubling of serum creatinine when compared with placebo or other antihypertensive agents. RAAS blockade with combined ACE inhibitor (ACEI) and angiotensin II receptor blocker (ARB) resulted in increased adverse events but not the expected synergistic effect. More therapies with different working mechanisms are needed.

Chinese medicine (CM) has been extensively used among patients with diabetes and DKD in Asia. Previous observational studies from Taiwan with 47876 and 24971 subjects showed that the use of add-on prescribed CM is associated with 40% reduction of mortality and 59% risk reduction of end-stage kidney disease, respectively. *Astragalus membranaceus*, commonly known as huang-qi, is the most frequently used CM or dietary herb for DKD. Systematic reviews showed that astragalus could enhance creatinine clearance, reduce albuminuria and reduce blood pressure among patients with CKD and DKD. Meta-analysis 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. *In vivo* and *in vitro* evidence suggested that astragaloside IV, an active ingredient of astragalus, could ameliorate podocyte apoptosis, foot process effacement, mesangial expansion, glomerulosclerosis and interstitial fibrosis through regulating the nuclear factor kappa B (NF-κB) and transforming growth factor beta 1 (TGF-β1) signalling pathways, which partly explained the renoprotective effect. Nevertheless, the methodological reporting and quality of the existing clinical trials were inadequate and further evaluation is needed. Based on our preliminary result of ongoing trials, CM formulations containing astragalus are likely to retard the progression of DKD. Considering the extensive current use of astragalus, clinical study could be considered before preclinical investigation as suggested by the WHO.

**METHODS/DESIGN**

**Objective**

This pragmatic clinical trial aims to evaluate the effectiveness of add-on astragalus on patients with type 2 diabetes with stage 2–3 chronic kidney disease and macroalbuminuria and to identify related response predictors for subsequent large-scale health services research.

**Study design**

Add-on, assessor-blind, parallel, pragmatic randomised controlled trial. The WHO Trial Registration Data Set (online supplemental appendix 1) and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (online supplemental SPIRIT checklist) are enclosed.

**Inclusion and exclusion criteria**

Patients with (1) type 2 diabetes for at least 5 years; (2) estimated glomerular filtration rate (GFR) ≥50 and < 90 mL/min/1.73 m² confirmed by repeated testing over 3 months calculated by the abbreviated Modification of Diet in Renal Disease (MDRD) study equation; (3) persistent macroalbuminuria with spot urine albumin-to-creatinine ratio (UACR) ≥300 mg/g confirmed by at least two consecutive first morning void urine samples; (4) age between 35 and 80 years old; (5) stable dose of antidiabetic agent(s) including insulin for at least 12 weeks and (6) stable dose of ACEI or ARB for at least 12 weeks will be recruited.

Patients will be excluded if with (1) UACR ≥5000 mg/g; (2) a known history of glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus or any suggestive evidence of non-diabetic glomerulopathy; (3) known history of kidney transplant; (4) concurrent severe disorders of heart, brain, liver and hematopoietic system, tumour, mental disorder; (5) deranged liver function; (6) poorly controlled blood pressure; (7) known history of intolerance or malabsorption of oral medications; (8) uncontrollable urinary infection; (9) experiencing pregnancy and (10) participating in other clinical trial(s) within 30 days.

**Sample size calculation**

Since 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. One hundred and eighteen patients (around 60 per group) are needed.
IF = $S_{\text{ult}}/S_{\text{obs}} = \sqrt{\frac{(n - 1)}{x_{1-\alpha, n-1}}}$

$N_{\text{adj}}/N_{\text{unadj}} \approx IF^2 \approx n_{\text{unadj}} \times IF^2$

$N \approx \left[2(Z_{\alpha/2} + Z_{\beta}^2) / (\mu_1 - \mu_2)^2\right]$

$Z_{1-\beta} = Z_{1-\alpha/2}(IF^2 - 1) + Z_{1-\beta} \times IF^{-1}$

where

IF=Inflation factor.

$S_{\text{ult}}$=SD of upper CI.

$S_{\text{obs}}$=Observed SD in pilot study.

$\alpha$=Chosen confidence level.

$\beta$=Nominal power set for main study.

$\beta$'=Actual power achieved for main study by using pilot SD.

$n$=Sample size of pilot study.

$N$=Sample size of main study.

$N_{\text{adj}}$=Sample size of main study with adjustment on SD.

$N_{\text{unadj}}$=Sample size of main study with no adjustment on SD.

The SD used for sample size calculation for large-scale main studies is often underestimated by small-scale pilot studies; therefore, an IF is needed for adjustment in sample size calculation.\(^{39,40}\) IF is calculated based on the size of pilot study and the confidence level of achieving at least the desired power in subsequent main studies. Therefore, the actual achieved power of the main studies depends on the nominal power set for the main study and the IF.

In order to be 95% confident (two-sided) that the main study achieves a power of 70% with nominal power set at 80% (i.e., a 10% power forfeiture), the IF should be controlled to less than 1.13. At IF=1.13, a sample size of 100 is therefore needed to attain 95% one-sided confidence that the main studies will achieve the nominal power to test the hypothesis of add-on astragalus could be more effective in stabilising the GFR among patients with DKD when compared with standard care. To allow a 15% attrition rate, a sample size of 118 patients is therefore needed for this pilot study.

Currently, there is limited evidence on the symptom-based response predictors of astragalus. A general recommendation for power estimation is to have 10 events per variable.\(^{41}\) From the previous systematic review, we estimate that around 60% of patients will have stabilised GFR after receiving astragalus.\(^{31}\) One hundred and eighteen subjects with 15% attrition will power up to six variables for the screening of predictors. A univariable screening on the 11 prespecified potential symptom-based predictors will be conducted to reduce the number of predictors for the subsequent multivariable regression analysis, in order to maximise the power of the regression analysis.

Recruitment and randomisation

Patients will be recruited from general and specialist outpatient clinics of Queen Mary Hospital, Queen Elizabeth Hospital, Hospital Authority Hong Kong East Cluster through consultations and the community via public health campaigns. The details of study will be explained by principal investigators (PIs) or co-investigators (Co-Is) before written consent is obtained from each participating patient. All patients will undergo a 2-week run-in period, during which the dosage of their medications will be stabilised. Blood and urine samples will be sent to an independent local laboratory for screening. Patients are considered eligible for the study if their liver functions are normal and fulfil the inclusion criteria. Recruitment started in July 2018 and the recruitment is ongoing.

A random sequence was generated and encrypted with computer by an independent staff of the University of Hong Kong and kept in sealed opaque envelopes. The password of the sequence is kept in a sealed, duly signed opaque envelop locked by research assistants (RA). The allocation sequence is concealed from PIs, Co-Is, CM physicians and all research staffs that are responsible for patient screening, randomisation or sample analysis. Eligible patients will be randomised 1:1 to either receive active intervention along with standard care or standard care alone. The allocation is masked from the outcome assessor (technicians from an independent laboratory). The study subjects could not be masked due to the nature of treatment. Since the primary clinical outcomes under investigation are objectively assessed and the outcome assessor is blinded, placebo effect and outcome measurement bias should be minimised. The flow of study is presented in figure 1. Under no circumstances the primary outcome assessors will be unblinded.

Intervention and control

The intervention under investigation is astragalus. Patients under intervention will receive astragalus daily on top of standard medical care for 48 weeks. The CM physicians will advise on the dose and possible adverse

Figure 1 The flow of research.

events of astragalus based on his/her professional knowledge. Existing literature supports a safe dosage of raw astragalus from 15 g/day to 50 g/day. According to the China Pharmacopeia, the recommended therapeutic dosage of astragalus is below 30 g/day. To ensure the safety of patients, CM physicians are reminded not to propose dosage exceeding 30 g/day. All patients will continue their standard medication and follow-up with the same consultation schedule with CM physicians. Standard care is used as control to best reflect the real-world practice and the future application scenario of this trial.44

Herbal safety
Soluble herbal granules prepared by PuraPharm (listed in US Pharmacopeia as dietary ingredient: VER-DI-PUR-09) are used. The production process is in strict compliance with standards of Good Manufacturing Practice. Fully registered CM physicians from the School of Chinese Medicine, The University of Hong Kong, will be responsible for the clinical diagnosis and prescription. After 4–6 weeks of randomisation, all patients will undergo liver function tests and renal function tests to monitor acute changes of renal and liver function.

Outcome measurement
The primary outcome measures are the changes of estimated GFR45 and UACR from baseline (week 0) to treatment endpoint (week 48). As the progression of kidney disease is slow, we believe reporting 1-year (48-week) change in GFR is necessary to avoid extrapolation while extended observation may lead to substantial attrition and is limited by resources. Secondary outcome measures include adverse events and changes in CKD stage, haemoglobin A1c (HbA1c), lipids, urinary monocyte chemotactic protein 1 (MCP-1) and urinary cystatin C from baseline to the midpoint (week 24) and the end of treatment.

Data collection
Patient demographics including age, gender, body mass index (BMI), duration of diabetes, other medical history and concurrent medications will be retrieved by the electronic clinical management system of hospital authority by Co-Is and RAs. Estimated GFR, UACR, HbA1c, lipids and liver function tests will be assessed by an independent laboratory (Chan & Hou Medical Laboratories Limited) which is accredited by College of American Pathologists, Royal College of Pathologists Australasia and Quality Control for Molecular Diagnostics. UK, MCP-1 and cystatin C will be assessed at lead PI’s research laboratory by an independent RA with commercially available kits. Blood pressure will be taken during consultation. Blood and urine samples will be taken at an overnight (>8 hours) fasting state.

Estimated GFR will be calculated using the MDRD equation with serum creatinine, age, ethnicity and gender. Clinical presentations and CM symptom-based diagnosis will be assessed in a structured consultation developed for this purpose. To ensure consistency and reliability of assessment and to minimise bias from investigators across the study, only three synchronised CM physicians will assess the patients.

A self-complete questionnaire will be distributed to the subjects to monitor adverse events, and they are advised to inform the PIs, Co-Is, CM physicians or RAs immediately if adverse events arise. All adverse events will be coded based on Common Terminology Criteria for Adverse Events (CTCAE) 5.0, following the recommendation of Consolidated Standards of Reporting Trials extension for Chinese herbal medicine formulas.46

Follow-up consultations will be held for all patients bi-weekly in the first month and monthly subsequently until the end of treatment for all patients. Minor adjustments are allowed based on clinical needs. Evaluation of outcomes will be performed at baseline, week 24 (treatment midpoint) and week 48 (end of treatment). The follow-up schedule is summarised in table 1.

Data management
A trial management committee (TMC) formed by lead PI, Co-Is and RAs will centralise all trial data. Co-Is and RAs will collect, clean and send the data to TMC weekly. All data will be double entered, secured and cleaned before analysis to prevent data entry errors. TMC will have regular meetings monthly to discuss the progress and double check the data of the trial. Only PI, Co-Is and regulatory bodies will have access to the patient data to protect data privacy. An independent Data and Safety Monitoring Board (DSMB) (VCH Chung, W Wong, JWF Yeung) has been established with expert in methodology, biostatistics and clinical medicine to monitor the progress of the trial, including adverse events and change in protocol. DSMB will have meetings one to two times a year. No competing interests have been reported from DSMB. Trial result will be published in academic journal and trial subjects will be notified.

Handling of withdraw and dropout
In order to maximise subjects’ compliance, we will provide a triple thorough consent process for all participants covering details of the study schedule, potential side effects of treatment and the responsibilities of the subjects. An independent e-mail account and a direct telephone line is available for this study to enable active communication with patients. Extra visits will be arranged for patients if necessary. To monitor the adherence of study medication, we will arrange irregular visits for patients and count the unfinished medication.

Termination criteria
The treatment will be terminated for a specific subject if he/she (1) develops serious adverse event (SAE); (2) develops hypersensitivity towards astragalus and (3) participates in other clinical trial. The whole study will be terminated under the following circumstances: (1) presence of clustered SAE(s) related to astragalus with
supportive evidence and (2) completion of all follow-up assessments.

SAE includes adverse events that result in death, require either hospitalisation or the prolongation of hospitalisation, are life-threatening, result in a persistent or significant disability/incapacity, result in a congenital anomaly/birth defect or events classified as grade 3 or above in CTCAE 5.0. Other important medical events, based on appropriate medical judgement, may also be considered SAEs if a patient's health is at risk and intervention is required to prevent an outcome mentioned.

**Data analysis**

Missing values will be imputed by multiple regression. The analysis will follow intention-to-treat principle that all randomised patients will be included in the analysis. STATA and GraphPad Prism will be used for the analysis.

Demographics will be presented as mean±SD or percentage. UACR will be log-transformed and reported as geometric means. Smoking history will be stratified into non-smoker, ex-smoker and current smoker. Rapid renal progression is predefined as a consecutive annual GFR drop of over 5mL/min/1.73 m² or a cumulative GFR drop of over 25mL/min/1.73 m² for 5 years.47 48 Differences in mean and proportion between groups will be tested by t-test and χ² test.

Mixed regression models will be used to compare the rate of change in estimated GFR and UACR. Analysis of covariance will be used to compare the adjusted mean of outcomes at week 48 between intervention group and control group with the corresponding baseline values as covariates. Data will be presented as the difference in adjusted means between the groups with 95% CI and the corresponding p value.

The adverse events will be recorded according to CTCAE 5.0 and categorised into five grades (grade 1: mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, no intervention indicated; grade 2: moderate, minimal, local or non-invasive intervention indicated, limiting age-appropriate instrumental activities of daily living; grade 3: severe or medically significant but not immediately life-threatening, hospitalisation or prolongation of hospitalisation indicated, disabling, limiting self-care activities of daily living; grade 4: life-threatening consequences, urgent intervention indicated and grade 5: death related to adverse events). The percentage of all adverse events with more than one case will be compared between groups. SAE will be analysed case by case descriptively.

To minimise type I error inflation, the analysis will follow a hierarchical approach in the order of (1) comparison of baseline to end of treatment on estimated GFR and UACR; (2) comparison of baseline to end of treatment on other outcome measurements; (3) comparison of baseline to treatment midpoints on estimated GFR and UACR and (4) comparison of baseline to treatment midpoints on other outcome measurements.

For the assessment of predictive factors as secondary analysis, the dependent variable will be the treatment response which is categorised into:

1. Improved or stabilised renal function, defined as estimated GFR after 48-week treatment being higher or equal to baseline.

### Table 1 Follow-up schedule

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Study period</th>
<th>Enrolment Before treatment</th>
<th>Allocation Week 0, Day 1</th>
<th>Post allocation—treatment period</th>
<th>Week 1–4 (±3 days)</th>
<th>After 4–6 weeks (±7 days)</th>
<th>After 24 and 48 weeks (±7 days)</th>
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<tr>
<td>Enrolment</td>
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<td>Renal and liver function tests, other biomarkers (blood and urine tests)</td>
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<td>Blood pressure, weight, hip–waist circumference</td>
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2. Non-responder, defined as patients having estimated GFR decreased at a rate of less than 5 mL/min/1.73 m² after 48-week treatment compared with baseline.
3. Rapid deteriorating renal function, defined as estimated GFR of more than 8 mL/min/1.73 m² after 48-week treatment compared with baseline.

Potential prognostic variables (baseline values) will include:
1. Demographics: age, gender, BMI, systolic blood pressure, history and duration of smoking and alcohol consumption.
2. Symptom-based diagnosis: presence of CM-based symptom-based subtype (eg, spleen and kidney qi deficiency) based on the presentation of standardised and commonly documented signs and symptoms.

All potential predictors will first be included into univariable regression models followed by multivariable stepwise regression analysis. Variables that are not significant at a 5% level will be excluded.

Subgroup analyses will be performed for (1) CKD stages stratified into stages 2, 3a and 3b; (2) UACR levels stratified by 100 mg/mmol; (3) gender and (4) age groups. Sensitivity analyses will be performed for (1) per-protocol cohort; (2) estimation of GFR by c-MDRD and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations; (3) missing data imputed with last-observation-carried-forward and (4) different analytical approaches (change score) and categorisations of primary outcomes.

**Patient and public involvement**
We conducted a focus group interview series to collate the experience and expectations of patients and clinicians (both conventional medicine and CM) on the study design (drug form, dosage, administration route, frequency, health services delivery and outcome measurement) for this trial. The study results will be disseminated to diabetes patient groups and the participants via public workshops and talks.

**ETHICS AND DISSEMINATION**
This study was approved and monitored by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West/East/Kowloon Central clusters (Ref: UW 16-553/HKEC-2019-026/REC (KC/KE)-19-0049/ER-4). The patient information sheet and consent form are enclosed in Appendix 2. Result will be disseminated as conference presentations and journal publications on completion.

**DISCUSSION**
Diabetes and DKD are significant public health burdens, and astragalus is the most used herbs among these patients with unclear clinical effectiveness. There is an urgent need to characterise the effect and the associated response predictors of astragalus to prevent unnecessary consumption and increase the cost-effectiveness of administration. Also, the assessment of response predictors of both biomarkers and symptom-based factors will facilitate the integration and clinical translation of generated evidence between conventional medicine and CM physicians. Based on our preliminary result of ongoing trials, CM formulations containing astragalus are likely to retard the progression of DKD. This trial aims to evaluate the effect of astragalus and identify related response predictors for more personalised application and further large-scale health services research.

To facilitate further meta-analysis with other clinical studies for wide range of audience, the inclusion/exclusion criteria, primary outcome measurement and the corresponding analyses are designed according to conventionally used parameters similar to other pharmacological studies. A responder analysis is included as secondary analysis to identify possible factors (including biomarkers and symptom-based diagnosis) that could lead to more personalised use of astragalus. Besides, we conducted a focus group interview series to explore the expectations of patients and clinicians (both conventional medicine and CM) to refine the study design for better clinical translation. The major limitation of this trial is the open-label nature. The study subjects could not be masked due to the nature of treatment. Since the clinical outcomes under investigation are objective and the outcome assessor is blinded, placebo effect and outcome measurement bias should be minimised. However, subjective outcomes including quality of life could not be assessed.

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**Contributors** KWC and SCWT conceived the study design. KWC and SCWT drafted the manuscript. All authors involved in the manuscript. The funding organisation had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript and decision to submit the manuscript for publication.

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Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix 1. World Health Organisation Trial Registration Dataset

<table>
<thead>
<tr>
<th>Data Category</th>
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<td>Contact for Public Queries</td>
<td>Prof TANG Chi-wai Sydney MD PhD</td>
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<td>Dr CHAN Kam-wa MSPH MD PhD</td>
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<tr>
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<td>Tel: +852 2255 3603</td>
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<td></td>
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</tr>
<tr>
<td>Scientific Title</td>
<td>Efficacy, Safety and Response Predictors of Adjuvant Astragalus for Diabetic Kidney Disease (READY) – An Add-on, Assessor-blind, Parallel, Pragmatic Randomised Controlled Trial</td>
</tr>
<tr>
<td>Countries of Recruitment</td>
<td>Hong Kong SAR, China</td>
</tr>
<tr>
<td>Health Condition(s) or Problem(s) Studied</td>
<td>Diabetic kidney disease</td>
</tr>
<tr>
<td>Intervention (s)</td>
<td>Active comparator: Standard medical care with angiotensin converting enzyme inhibitor or angiotensin receptor blocker and oral hypoglycemic agents and/or insulin at stable dose</td>
</tr>
<tr>
<td></td>
<td>Experimental arm: Semi-individualised dosage of astragalus on top of standard medical care</td>
</tr>
<tr>
<td>Key Inclusion and Exclusion Criteria</td>
<td>Ages eligible for study: between 35 and 80 years old</td>
</tr>
<tr>
<td></td>
<td>Gender eligible for study: Both</td>
</tr>
</tbody>
</table>
Healthy volunteers: Not accepted

Inclusion Criteria:

- diagnosed with type 2 diabetes for at least 5 years;

- with an estimated glomerular filtration rate (GFR) ≥30 <90 mL/min/1.73m² confirmed with repeat testing over three or more months calculated by the abbreviated MDRD study equation;

- persistent macroalbuminuria with spot urine albumin-to-creatinine ratio (UACR) ≥ 300 mg/g confirmed by at least 2 out of 3 consecutive first morning void urine samples;

- on stable dose of anti-diabetic drug including insulin for 12 weeks;

- on stable dose of angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker for 12 weeks; and

- willing and able to give written informed consent

Exclusion Criteria:

- with known history of glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, any suggestive evidence of nondiabetic glomerulopathy;

- with known history of kidney transplant;

- with concurrent severe disorders of heart, brain, liver, and hematopoietic system, tumor and mental disorder;

- with deranged liver function;

- with poorly controlled blood pressure;

- with known history of intolerance or malabsorption of oral medications;

- with uncontrollable urinary infection;

- experiencing pregnancy; or
- participating in other clinical trial within 30 days

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Interventional</th>
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<tbody>
<tr>
<td>Allocation: randomised</td>
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<tr>
<td>Intervention model: parallel assignment (2 arms)</td>
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</tr>
<tr>
<td>Masking: Open label (Accesscior of primary outcome measures blinded)</td>
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<tr>
<td>Primary purpose: Treatment</td>
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<tr>
<td>Phase: II/III</td>
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<tr>
<td>Allocation concealment: Sealed opaque envelope prepared by an independent technical staff</td>
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<tr>
<td>Sequence generation: computer generated random sequence</td>
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</table>

<table>
<thead>
<tr>
<th>Date of First Enrollment</th>
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<tr>
<td>Target Sample Size</td>
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<tr>
<td>Recruitment Status</td>
<td>Recruiting</td>
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<tr>
<td>Primary Outcome(s)</td>
<td>Changes in estimated glomerular filtration rate and spot urine to albumin ratio (time frame: 48 weeks)</td>
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<tr>
<td>Key Secondary Outcome(s)</td>
<td>Adverse events, changes in, glycated haemoglobin, lipids, blood pressure and other biomarkers</td>
</tr>
</tbody>
</table>
Appendix 2. Sample Consent form

Patient/Subject Information Sheet

1. STUDY TITLE
Efficacy, safety and response predictors of adjuvant astragalus for diabetic kidney disease (READY) – An open-label randomised controlled trial with responder regression analysis

2. INVITATION PARAGRAPH
You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your family doctor if you wish to. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

3. WHAT IS THE PURPOSE OF THE STUDY?
Modern pharmacologic therapy using blockers of angiotensin II is unable to fully suppress the progression of chronic kidney disease (CKD). As a result, many patients progress to end-stage kidney disease and require either dialysis or transplantation. Recently, research data shows that astragalus has anti-fibrotic effect, slower the progression to kidney disease and have been using in addition to routine medical care in Hong Kong. However, the actual pharmacological and therapeutic effect of astragalus are unclear. The present study lasting 48 weeks aims to investigate whether astragalus consumption stabilises renal function and reduces albuminuria.

4. WHY HAVE I BEEN CHOSEN?
You have CKD with unsatisfactory proteinuria control despite angiotensin blockade therapy, and are now being invited to participate in this study to investigate the potential beneficial effect of astragalus that is currently widely used in Hong Kong.

5. DO I HAVE TO TAKE PART?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.
6. WHAT WILL HAPPEN TO ME IF I TAKE PART?
You will be randomised by computer after thorough assessment to either receive guidance on astragalus consumption in addition to your standard medications or continue standard medications. The observation period of this study is 48 weeks, and you will be followed up at the clinic in the usual manner, but with additional blood and urine tests as appropriate. You will need to attend 6 extra clinic visits for Chinese medicine consultation in addition to your usual visits over the next 48 weeks.

7. WHAT DO I HAVE TO DO?
There are no lifestyle restrictions by participating in this study, except for the need of practicing contraception. As you have CKD, you will be given dietary advice on salt and protein restriction which are necessary even if you are not participating in this study. You will take the astragalus on top of your therapy for your present condition.

8. WHAT IS THE DRUG OR PROCEDURE THAT IS BEING TESTED?
Astragalus has been widely consumed for years in Hong Kong although with limited clinical evidence. According to existing best available evidence, astragalus has anti-fibrotic effect and could slower the progression to kidney disease. Currently, no adverse events have been confirmed to associate with the use of astragalus.

9. WHAT ARE THE ALTERNATIVES FOR DIAGNOSIS OR TREATMENT?
An alternative treatment option of chronic kidney disease is standard medical care with angiotensin receptor blocker or angiotensin converting enzyme inhibitor alone.

10. WHAT ARE THE SIDE EFFECTS OF TAKING PART?
Astragalus is generally well tolerated. There are no known side effects in addition to those of conventional treatment when astragalus is being used within the reference range of Pharmacopeia of China. Nevertheless, astragalus may have unknown side effects. Full evaluation will be performed and adequate monitoring will be exercised once you start taking it. You will need to attend 6 extra clinic visits in addition to your usual visits over the next 48 weeks. Any claims on loss or injury attributable to the study will be arranged by the University of Hong Kong.

11. WHAT ARE THE DISADVANTAGES AND RISKS OF TAKING PART?
The safety of the astragalus to the human fetus is unclear, therefore women with child-bearing potential must practice contraception.

12. WHAT ARE THE BENEFITS OF TAKING PART?
We hope that astragalus will help you. However, this cannot be guaranteed. The information we get from this study may help us treat future patients with CKD better.

13. WHAT IF NEW INFORMATION BECOMES AVAILABLE?
Sometimes during the course of a research project, new information becomes available about astragalus that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

14. WHAT HAPPENS WHEN THE RESEARCH STUDY STOPS?
After the study stops, you will be advised whether or not to continue with astragalus according to clinical need. Astragalus will not be provided for free.

15. WHAT IF SOMETHING GOES WRONG?
Any claims on loss or injury attributable to the study will be arranged by the University of Hong Kong. If you are harmed due to someone’s negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal health service complaints mechanisms may be available to you.

16. WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?
You have the rights of access to personal data and publicly available study results, if and when needed.

Under the laws of Hong Kong (in particular the Personal Data (Privacy) Ordinance, Cap 486), you enjoy or may enjoy rights for the protection of the confidentiality of your personal data, such as those regarding the collection, custody, retention, management, control, use (including analysis or comparison), transfer in or out of Hong Kong, non-disclosure, erasure and/or in any way dealing with or disposing of any of your personal data in or for this study. For any query, you should consult the Privacy Commissioner for Privacy Data or his office (Tel No. 2827 2827) as to the proper monitoring or supervision of your personal data protection so that your full awareness and understanding of the significance of compliance with the law governing privacy data is assured.

By consenting to participate in this study, you expressly authorize:
• the principal investigator and his research team and the ethics committee responsible for overseeing this study to get access to, to use, and to retain your personal data for the purposes and in the manner described in this informed consent process; and
• the relevant government agencies (e.g. the Hong Kong Department of Health) to get access to your personal data for the purposes of checking and verifying the integrity of study data and assessing compliance with the study protocol and relevant requirements.

17. WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?
The results of this study will be published in a medical journal. Your personal information will be kept confidential.

18. WHO IS ORGANISING AND FUNDING THE RESEARCH?
This study is supported by the Health and Medical Research Fund and you do not need to pay any extra cost. Your doctor will not be paid for including you in this study.

19. WHO HAS REVIEWED THE STUDY?
The Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster has reviewed and approved this study. After recruitment, each patient will receive HK$150 for each blood/urine investigation visit related to this study as travel support.

20. CONTACT FOR FURTHER INFORMATION
In case of enquiry, you may contact Mr Chris Chan or Prof Sydney Tang at 2255 3207. You will be given a copy of this information sheet and a signed consent form to keep. Thank you for taking part in this study!

From the Division of Nephrology
Department of Medicine
University of Hong Kong
Queen Mary Hospital
PATIENT/SUBJECT CONSENT FORM

Title of Project: Efficacy, safety and response predictors of adjuvant astragalus for diabetic kidney disease (READY) – An open-label randomised controlled trial with responder regression analysis

Name of Researcher: Prof Sydney C.W. Tang

1. I confirm that I have read and understood the information sheet dated __/__/__ for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

4. I agree to take part in the above study.

_______________________________  __________________________  __________________________
Name of patient  Date  Signature

_______________________________  __________________________  __________________________
Name of Witness (if applicable)  Date  Signature

_______________________________  __________________________  __________________________
Name of person taking consent (if different from researcher)  Date  Signature

_______________________________  __________________________  __________________________
Researcher  Date  Signature

Copies to:
☐ Patient/Subject
☐ Researcher’s File
☐ Hospital Record
# SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

## Administrative information

<table>
<thead>
<tr>
<th>Section/item</th>
<th>Item No</th>
<th>Description</th>
<th>Addressed on page number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td>1</td>
<td>Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</td>
<td>1</td>
</tr>
<tr>
<td>Trial registration</td>
<td>2a</td>
<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>All items from the World Health Organization Trial Registration Data Set</td>
<td>Appendix 1</td>
</tr>
<tr>
<td>Protocol version</td>
<td>3</td>
<td>Date and version identifier</td>
<td>Appendix 1</td>
</tr>
<tr>
<td>Funding</td>
<td>4</td>
<td>Sources and types of financial, material, and other support</td>
<td>Appendix 1</td>
</tr>
<tr>
<td>Roles and</td>
<td>5a</td>
<td>Names, affiliations, and roles of protocol contributors</td>
<td>Appendix 1</td>
</tr>
<tr>
<td>responsibilities</td>
<td>5b</td>
<td>Name and contact information for the trial sponsor</td>
<td>Appendix 1</td>
</tr>
<tr>
<td></td>
<td>5c</td>
<td>Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities</td>
<td>27, 28</td>
</tr>
<tr>
<td></td>
<td>5d</td>
<td>Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)</td>
<td>17, 28</td>
</tr>
</tbody>
</table>
### Introduction

**Background and rationale**

6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

7-9

6b Explanation for choice of comparators

8, 9, 14, 15

**Objectives**

7 Specific objectives or hypotheses

10

**Trial design**

8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

1, 10

### Methods: Participants, interventions, and outcomes

**Study setting**

9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

13

**Eligibility criteria**

10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

10, 11, 14

**Interventions**

11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

14, 15

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

17, 18

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

18

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

10, 14

**Outcomes**

12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

15

**Participant timeline**

13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for _Figure 1, Table 1_ participants. A schematic diagram is highly recommended (see Figure)
<table>
<thead>
<tr>
<th>Sample size</th>
<th>Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment</td>
<td>Strategies for achieving adequate participant enrolment to reach target sample size</td>
</tr>
</tbody>
</table>

**Methods: Assignment of interventions (for controlled trials)**

**Allocation:**

<table>
<thead>
<tr>
<th>Sequence generation</th>
<th>Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment mechanism</td>
<td>Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned</td>
</tr>
</tbody>
</table>

**Implementation:**

<table>
<thead>
<tr>
<th>Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions</th>
</tr>
</thead>
</table>

**Blinding (masking):**

<table>
<thead>
<tr>
<th>Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how</th>
</tr>
</thead>
<tbody>
<tr>
<td>If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial</td>
</tr>
</tbody>
</table>

**Methods: Data collection, management, and analysis**

<table>
<thead>
<tr>
<th>Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols</td>
</tr>
<tr>
<td>Section</td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Data management</td>
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<tr>
<td>Statistical methods</td>
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<tr>
<td>Methods: Monitoring</td>
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<tr>
<td>26a</td>
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<td>31a</td>
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<td>31b</td>
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<tr>
<td>31c</td>
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**Appendices**

<table>
<thead>
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<th>Item</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>Model consent form and other related documentation given to participants and authorised surrogates</td>
<td>Appendix 2</td>
</tr>
<tr>
<td>33</td>
<td>Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license."