Micro-Particle Curcumin for the Treatment of Chronic Kidney Disease-1: Study Protocol for a Multicenter Clinical Trial

Matthew A. Weir¹,²,³, Michael Walsh⁴,⁵, Meaghan S. Cuerden², Jessica M. Sontrop², Laura C. Chambers², and Amit X. Garg¹,²,³

Abstract

Background: The progression to end-stage renal disease (ESRD) is the most important complication of chronic kidney disease (CKD). Patients with ESRD require dialysis or transplantation to survive, incur numerous complications, and have high mortality rates. Slowing the progression of CKD is an important goal. Unfortunately, even when current treatments are appropriately applied, patients with CKD still progress to ESRD. Current treatments do not address the inflammation and fibrosis that mediate progression to ESRD, but micro-particle curcumin, a natural health product, has both anti-inflammatory and anti-fibrotic properties and may be an effective treatment for patients with CKD.

Objective: Micro-particle curcumin for the treatment of CKD-1 (MPAC-CKD-1) will measure the effect of micro-particle curcumin on 2 important markers of CKD progression: albuminuria and estimated glomerular filtration rate (eGFR). Efficacy in either of these markers will justify a larger, international trial to investigate micro-particle curcumin’s ability to lower the risk of ESRD in patients with CKD.

Design: MPAC-CKD-1 is a multicenter, double-blind prospective randomized controlled trial.

Setting: Four kidney disease clinics in Ontario, Canada (3 in London and 1 in Hamilton).

Patients: We will enroll patients with CKD, defined by an eGFR between 15 and 60 mL/min/1.73 m² and a daily albumin excretion of more than 300 mg (or a random urine sample albumin-to-creatinine ratio more than 30 mg/mmol).

Measurements: We will measure changes in the co-primary outcomes of urinary albumin-to-creatinine ratio and eGFR at 3 months and 6 months. We will also measure compliance, safety parameters, and changes in health-related quality of life.

Methods: Participants will be randomly assigned to receive micro-particle curcumin 90 mg once daily or matching placebo for 6 months. We will enroll at least 500 patients to exclude clinically meaningful 6-month changes in these 2 co-primary outcomes (16% difference in albuminuria, and a 2.3 mL/min/1.73 m² between-group difference in the 6-month change in eGFR, at a two-tailed alpha of 0.025, power of 0.80).

Results: Patient enrollment began on October 1, 2015, with 414 participants randomized as of July 2018. We expect to report the results in 2020.

Limitations: MPAC-CKD-1 is not powered to assess outcomes such as the need for renal replacement therapy or death.

Conclusions: MPAC-CKD-1 is a multicenter, double-blind prospective randomized controlled trial designed to test whether micro-particle curcumin reduces albuminuria and slows eGFR decline in patients with albuminuric CKD. MPAC-CKD-1 will also test the feasibility of this intervention and inform the need for a future larger scale trial (MPAC-CKD-2).

Trial registration: MPAC-CKD-1 is registered with U.S. National Institutes of Health at clinicaltrials.gov (NCT02369549). Protocol version 2.0, December 6, 2014.

Abridged

Contexte: La progression vers l’insuffisance rénale terminale (IRT) est la plus importante complication de l’insuffisance rénale chronique (IRC). Les patients atteints d’IRT dépendent de la dialyse ou de la transplantation pour survivre. Ces patients subissent de nombreuses complications et font face à des taux de mortalité très élevés. Ralentir la progression de la maladie est un objectif majeur. Malheureusement, même lorsque les traitements sont prodigués correctement, certains patients atteints de néphropathie chronique progressent vers l’IRT. Les traitements actuels ne parviennent pas à réduire l’inflammation et la fibrose qui médient cette progression. Les microparticules de curcumine, un produit de santé naturel qui...
possède des propriétés anti-inflammatoire et anti-fibrotiques, pourraient s’avérer un traitement efficace pour les patients atteints d’IRC.

**Objectif:** L’étude MPAC-CKD-1 mesurera l’effet des microparticules de curcumine sur deux marqueurs importants de la progression de la maladie : l’albuminurie et le débit de filtration glomérulaire estimé (DFGe). L’efficacité des microparticules de curcumine sur l’un ou l’autre de ces marqueurs justifiera la conduite d’un essai international à plus grande échelle qui étudiera leur capacité à réduire le risque de progression vers l’IRT chez les patients atteints d’IRC.

**Type d’étude:** L’étude MPAC-CKD-1 est un essai multicentrique prospectif, contrôlé, à répartition aléatoire et à double insu.

**Cadre:** Quatre cliniques spécialisées en néphropathie de l’Ontario, au Canada (trois à London et une à Hamilton).

**Sujets:** Seront recrutés les patients atteints d’IRC dont le DFGe se situe entre 15 et 60 ml/min/1,73 m$^2$ et l'excrétion d'albumine quotidienne à plus de 300 mg (ou dont un échantillon d’urine présente un rapport albumine/créatinine de plus de 30 mg/mmol).

**Mesures:** Les changements dans les deux principaux résultats (DFGe et rapport albumine/créatinine urinaire) seront mesurés à trois mois et à six mois. Seront également mesurés la conformité, les paramètres relatifs à l’innocuité et les changements dans la qualité de vie du patient en lien avec sa santé.

**Méthodologie:** Un traitement d’une durée de six mois (dose quotidienne de 90 mg de curcumine ou un placébo) sera attribué de façon aléatoire aux participants. Un minimum de 500 patients sera inclus à l’étude afin d’exclure les changements cliniquement significatifs survenant au cours des six mois pour les deux principaux résultats étudiés (une différence de 16 % de l’albuminurie et une différence de 2,3 ml/min/1,73 m$^2$ du DFGe dans les six mois entre les deux groupes, avec un alpha bilatéral de 0,025 à la puissance 0,80).

**Résultats:** Le recrutement des patients a débuté le 1er octobre 2015 et en date de juillet 2018, 414 participants avaient été répartis. La publication des résultats est prévue en 2020.

**Limites:** L’étude MPAC-CKD-1 n’est pas conçue pour mesurer des résultats tels que le besoin de recourir à une thérapie de remplacement rénal ni pour répertorier le taux de mortalité.

**Conclusion:** L’étude MPAC-CKD-1 est un essai multicentrique prospectif, contrôlé, à répartition aléatoire et à double insu, conçu pour mesurer l’effet des microparticules de curcumine chez les patients atteints d’IRC albuminurique. On veut pouvoir observer soit une réduction de l’albuminurie, soit un ralentissement du déclin du DFGe. L’étude MPAC-CKD-1 vise également à tester la faisabilité de cette intervention et à éclairer le besoin de procéder à un essai futur à plus grande échelle (MPAC-CKD-2).

**Keywords**
CKD (chronic kidney disease), randomized controlled trial, albuminuria

Received August 2, 2018. Accepted for publication September 24, 2018.

**What was known before**
Curcumin, a component of the spice turmeric, has anti-inflammatory and anti-fibrotic properties. Animal models and small-scale human studies suggest that curcumin may slow the progression of chronic kidney disease.

**What this adds**
By randomizing at least 500 patients with albuminuric chronic kidney disease to 90 mg per day of micro-particle curcumin or placebo, we will determine its effects on albuminuria and renal function. This trial will also determine the need for, and the feasibility of, a large-scale trial to assess clinically meaningful end points.

**Introduction**
Chronic kidney disease (CKD) is defined by an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m$^2$ or evidence of persistent kidney damage, such as excessive

---

1Division of Nephrology, Department of Medicine, Western University, London, ON, Canada
2Kidney Clinical Research Unit, London Health Sciences Centre, University Hospital, London, ON, Canada
3Department of Epidemiology and Biostatistics, Western University, London, ON, Canada
4Division of Nephrology, Department of Medicine, McMaster University, Hamilton, ON, Canada
5Population Health Research Institute, Hamilton Health Sciences, McMaster University, Hamilton, ON, Canada

**Corresponding Author:**
Matthew A. Weir, Kidney Clinical Research Unit, London Health Sciences Centre, University Hospital, Room A10-213, 339 Windermere Road, London, ON, Canada N6A 5A5.
Email: matthew.weir@lhsc.on.ca
albuminuria. CKD is associated with significant morbidity and mortality but the most important complication of CKD is the progression to kidney failure (end-stage renal disease, ESRD). Patients who progress to ESRD require dialysis or transplantation to survive. They experience numerous complications, have high mortality rates,1 and their care is very expensive.2 Therefore, preventing or slowing the progression from CKD to ESRD is an important clinical and research goal. Currently, few treatments have been proven to slow progression, and even when these therapies are appropriately applied, many patients still progress to ESRD.3 This may be explained in part by inflammation and fibrosis, 2 processes that play a role in the progression of CKD,4,2 but are not addressed by current therapies.

Curcumin, a component of the dietary spice turmeric, has proven anti-inflammatory and anti-fibrotic properties (Supplement Figure S1) and has been shown to mitigate renal damage in multiple animal models of CKD (Supplement Table S1).5-9 The ability of curcumin to reduce albuminuria in humans is supported by 2 trials in patients with nephrotic-range proteinuria.10-12 However, these trials were small and patients were treated with turmeric, of which curcumin is only a small component. Furthermore, curcumin in its traditional form has very poor bioavailability.13-15 To increase patients’ exposure to curcumin, we chose to study a micro-particle formulation that is 27 times more bioavailable.16

Micro-particle curcumin for the treatment of CKD-1 (MPAC-CKD-1) is a double-blind, placebo-controlled randomized trial that will measure the effect of micro-particle curcumin on 6-month changes in 2 important markers of CKD progression: albuminuria and eGFR. Positive effects in either of these markers will justify a larger, international trial that will determine micro-particle curcumin’s ability to decrease the risk of ESRD in patients with CKD.

Methods

This protocol is presented according to the SPIRIT guidelines (see supplemental materials).17

Study Setting

We will coordinate this trial through the Lilibeth Caberto Kidney Clinical Research Unit at London Health Sciences Centre in London, Ontario. The trial steering committee is comprised of AX Garg and MA Weir, who will also provide outcome and adverse event adjudication. We will identify patients through 3 clinics in London, Ontario, Canada, and 1 clinic in Hamilton, Ontario, Canada. In each clinic, attending physicians will introduce the study and interested patients will meet with research coordinators to discuss the trial in detail. Those who are eligible and willing to participate will provide written, informed consent prior to randomization.

Eligibility Criteria

We will recruit patients with advanced CKD but who have not yet progressed to an irreparable stage. We will enroll patients with an eGFR between 15 and 60 mL/min/1.73 m² and overt albuminuria, defined by a 24-hour urine collection with more than 300 mg of protein or a random urine albumin-to-creatinine ratio greater than 30 mg/mmol (265.2 mg/g). We will exclude patients with conditions that may potentially be exacerbated by the use of micro-particle curcumin (active peptic ulcer disease, hepatobiliary disease, history of significant bleeding) or who take medications that may interact with micro-particle curcumin (Table 1).

Interventions

We will randomly assign patients to receive either micro-particle curcumin or matching placebo. Micro-particle curcumin will be administered at 90 mg per day (three 30 mg capsules once daily) for 6 months. Our rationale for the dosage selection is presented in the supplemental materials. The dose will remain constant over the study period. Randomization to micro-particle curcumin or matching placebo will occur in a 1:1 ratio. Balanced block randomization will be conducted using a computerized algorithm with variable block sizes and treatment allocation will be stratified by site (3 sites in London, 1 site in Hamilton) and by baseline diabetes mellitus status. After providing written informed consent, patients will be allocated randomly by means of a 24-hour online computerized system to maintain allocation concealment. Participants, investigators, and all research staff will remain unaware of the treatment allocation. Unblinding will occur in the setting of a severe adverse reaction in which the treating physician believes the investigational product may have a role in the patient’s condition or treatment.

Concomitant Care

Hypertension and proteinuria will be managed according to the Canadian Hypertension Education Program guidelines,18 which suggest treatment with an angiotensin-converting-enzyme inhibitor or an angiotensin receptor blocker. Patients not taking one of these medications require the reason why to be documented in the medical record. The doses of these medications may be reduced or the drug may be stopped during the course of the study, but the medical indication prompting that decision (eg, hyperkalemia) must be documented. We will not impose dietary restrictions because dietary sources of curcumin provide exceedingly small amounts of curcumin19,20; however, we will ask patients to refrain from using over-the-counter curcumin or turmeric supplements and document any use at each study visit.
Outcomes

Primary outcomes. We will assess the 6-month change in 2 co-primary outcomes: the change in albuminuria, and the change in eGFR. Albuminuria will be measured using albumin-to-creatinine ratios from first morning urine samples. The eGFR will be calculated using the CKD-EPI formula, which includes patient age, sex, race (African or non-African), and the serum creatinine concentration.

Secondary outcomes

Glycemic control. We will assess glycemic control using the percentage of glycated hemoglobin at baseline, 3 months, and 6 months among patients with diabetes mellitus (diabetes mellitus was a stratification variable in the randomization). Curcumin use has been associated with improved glycemic control in animal models, and human studies.

Study agent discontinuation and safety. Because MPAC-CKD-1 may inform the launch of subsequent larger trials, a better understanding of the tolerability of micro-particle curcumin in the CKD population is necessary. We will test protocol compliance through pill counts and interviews at each follow-up visit. Side effects will be assessed using standardized case report forms at each visit.

Renal failure composite (eGFR loss of $\geq 30\%$, or ESRD, or death). We expect less than 10% of participants will experience these outcomes by 6 months. Although we will not have adequate statistical power to detect a meaningful effect of curcumin on these outcomes, we will document any trends to inform the expected event rate for future studies. We will define ESRD as an eGFR $< 15 \text{mL/min}/1.73 \text{m}^2$ or the initiation of renal replacement therapy, which includes dialysis or transplantation.

Health-related quality of life. We will compare health-related quality of life scores determined by the RAND version of the Short Form-36 (SF-36) questionnaire administered at baseline and 6 months. We will compare changes in both the physical composite score and the mental composite score. Beyond preservation of kidney function are several other potential mechanisms by which curcumin may benefit quality of life, including potential benefits on depression and chronic pain.

Additional outcomes

Serum curcumin levels. The strength of previously identified relationships between traditional curcumin exposure and clinical outcomes has been limited by the difficulty in achieving measurable serum curcumin levels. To confirm the improved bioavailability reported with micro-particle curcumin, and to strengthen any relationship between micro-particle curcumin and any outcomes we identify, we will measure serum trough levels of curcumin and its major metabolites in the first 25 participants randomized.

Recruitment

To ensure we can achieve this recruitment goal, we have assessed the number of provisionally eligible patients managed in the 4 clinics involved in this trial and have gauged the success of a recently conducted trial with similar inclusion criteria. In addition, we have worked closely with research
Figure 1. Participant timeline.

Note. eGFR = estimated glomerular filtration rate; SF-36 = Short Form-36; UACR = urinary albumin-to-creatinine ratio.
coordinators to remove possible barriers to enrollment and streamline the data collection process.

**Data Collection Methods**

We will gather outcome measures 3 months and 6 months after randomization. To reduce the variability in the urinary albumin-to-creatinine ratio, we will take the mean of first morning urine samples collected on 2 consecutive days. In our previous work, we determined that the mean of two samples substantially reduced the standard deviation of the log-transformed percentage change from 0.59 to 0.49. We will calculate the eGFR rates using the measured plasma creatinine concentrations. These will be measured at central hospital-based laboratories using standardized enzymatic colorimetric methods.

**Nonadherence**

Patients who miss taking the investigational study medication over 7 or more days during any 4-week period will meet with an investigator to discuss ways of improving adherence. We will catalogue the reasons for nonadherence and the strategies used to overcome them. Patients who do not attend study visits will be contacted and encouraged to comply with the protocol in whatever way they can. Until the study ends or the participant withdraws consent, we will attempt to reach them 3 times within each 4-week period to determine their status. In extenuating circumstances, we will contact the patient’s family physician to determine the patient’s vital status.

**Statistical Methods**

**Sample size.** Most physicians would view a 15% to 25% reduction in albuminuria as evidence of a promising treatment effect. Such was the case for ACE inhibitors and angiotensin receptor blockers, which showed a reduction in albuminuria of 15% to 50% and were later proven to reduce the risk of mortality and ESRD.\(^{29-32}\) In our preliminary work on urinary albumin-to-creatinine ratio testing, we found patients eligible for MPAC-CKD-1 had a mean initial urinary albumin-to-creatinine ratio of 128.3 mg/mmol.\(^{28}\) Over 3 months, we observed a mean increase in the urinary albumin-to-creatinine ratio of 30.7 mg/mmol and found the standard deviation of the change to be 69.2 mg/mmol. Using these data, enrolling 250 patients per group will allow an 87% power (\(\alpha = 0.025\)) to exclude a difference of 21 mg/mmol. To allow for loss to follow-up, we expect to recruit up to an additional 75 patients to reach a minimum of 250 patients per arm with complete follow-up data. For changes in eGFR, we will have 90% power (\(\alpha = 0.025\)) to exclude a difference of 2.3 mL/min/1.73 m\(^2\) between treatment and control groups (using a standard deviation of 4 mL/min/1.73 m\(^2\)). This estimate is based on a reported average decline in eGFR in albuminuric CKD patients of 2 to 4 mL/min/1.73 m\(^2\)/year (with a standard deviation of 3-4 mL/min/1.73 m\(^2\)/year).\(^{33,34}\)

**Primary outcome.** We will conduct all primary analyses according to the intention-to-treat principle. Significance testing will be conducted with a two-sided alpha level of 0.05/2 using Hochberg adjustment for 2 simultaneous primary end points.\(^{35}\) We will use two-sample \(t\) tests to compare changes in the co-primary outcomes.\(^{32,36}\) Missing data will be handled using model-based multiple imputation methods (and sensitivity analyses will be performed to confirm that conclusions are not sensitive to assumptions about the missing-data mechanism);\(^{37}\) the albumin-to-creatinine ratio data collected at the 3-month visit will be included in the imputation model.

**Secondary outcomes.** We will use a two-sample \(t\) test to compare changes in hemoglobin A1c between the 6-month and baseline values. The risk of the composite outcome of loss of \(\geq 30\%\) of baseline eGFR, ESRD, or death will be compared between groups using logistic regression analysis. The proportions of patients discontinuing study capsules and experiencing adverse events will be compared between groups using the chi-square test.

**Baseline characteristics.** Randomization reliably removes random differences between treatment groups when at least 1000 participants are included.\(^{38}\) With the size of our sample, it is possible that imbalances may arise between the treatment groups on important characteristics that may influence outcomes. We will record baseline characteristics pertinent to the progression of CKD and adjust the final point estimates of risk for these variables using linear regression analysis. Characteristics that will be included in the multivariable regression model are the following: age, sex, tobacco use, blood pressure, glycemic control, use of angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers, use of aldosterone antagonists. Sodium-glucose co-transporter-2 (SGLT-2) inhibitors were approved for use in Canada in May 2014, and gained provincial formulary coverage in 2015. Because these medications have been shown to reduce albuminuria, we will record these use\(^{39,40}\); however, given their minimum eGFR cut off of 45 mL/min/1.73 m\(^2\), we anticipate that they will not be commonly used in our population.

**Other analyses.** We will conduct an exploratory per-protocol analysis consisting of patients with no major protocol violations and who were exposed to their randomly assigned treatment for a minimum of 3 months. We will also conduct a subgroup analysis based on a higher or lower estimated risk of kidney failure (using the kidney failure risk equation).\(^{41}\)

**Results**

MPAC-CKD-1 began enrollment on October 1, 2015, and has randomized 414 participants as of July 2018. We expect to complete enrollment in 2019 and report the results publicly in 2020.
Discussion

Micro-particle curcumin holds a great deal of promise as a treatment to slow the progression of CKD because of its anti-inflammatory and anti-fibrotic properties.

*In vitro* experiments using a variety of cell lines have shown that curcumin exposure attenuates the activation of nuclear factor-kappa B (NF-κB). Activation of NF-κB is a pivotal regulatory step in the inflammatory process that leads to the elaboration of interleukin-1 (IL-1), IL-2, IL-6, tumor necrosis factor-alpha (TNF-α), and monocyte chemotactic protein-1 (MCP-1). By blocking its activation, curcumin acts as a potent anti-inflammatory agent. The conversion of functional tissue to scar is a hallmark of progressive CKD. Transforming growth factor-beta (TGF-β) is one of the most important mediators in this process. In a variety of *in vitro* settings, curcumin has been shown to lessen the effect of TGF-β through inhibition of its molecular signaling, activation of endogenous inhibitors, thereby resulting in less scar formation.

Animal models of CKD also support the effectiveness of curcumin exposure. Soetikno et al reported that compared with placebo, diabetic rats fed with curcumin 100 mg/kg per day for 8 weeks had far less scar tissue in their kidneys and expressed lower levels of TGF-β. In two related studies, Ghosh et al showed that rats with 5/6 nephrectomies who consumed 75 mg/kg curcumin per day had less proteinuria, better kidney function, more normal appearing renal histology, and lower levels of NF-κB and TNF-α than those on a placebo diet. Follow-up study of Ghosh et al showed that this benefit was realized even when curcumin treatment was delayed until after the appearance of proteinuria (a more clinically relevant timing of curcumin exposure). Sharma et al found similar effects in diabetic rats and demonstrated a dose-response.

Two small trials have tested curcumin supplementation in patients with kidney impairment. In the study most applicable to MPAC-CKD-1, Khajehdehi et al randomized 40 patients with diabetic CKD to receive placebo or turmeric (0.5 g 3 times daily; approximately equivalent to 66 mg of curcumin per day) for 2 months. Both groups began the study with approximately 4.5 g of daily proteinuria. After only 2 months of treatment, the turmeric group had a 39% reduction in proteinuria while the placebo group’s proteinuria remained unchanged. The treatment group experienced significant reductions in serum levels of TGF-β and TNF-α. In the second trial of patients with lupus nephritis, turmeric supplementation again decreased proteinuria significantly compared with placebo.

MPAC-CKD-1 is the next step in assessing micro-particle curcumin’s potential to slow the progression of CKD. If meaningful changes in our surrogate outcome measure are observed, this will justify a larger, international trial equipped to test curcumin’s ability to lower the risk of ESRD.

Acknowledgments

We would like to thank Darek Godzvik for the development and maintenance of the trial database and Virginia Schumann for her financial management and assistance in obtaining Health Canada approval for this trial.

Availability of Data and Materials

The study investigators will have access to the final trial data set. We do not plan to make data sets available to the public.

Data Monitoring

The Data Safety Monitoring Committee (DSMB) will be comprised of external content experts with experience in clinical trials. The DSMB will review unblinded safety data once 50% of patients have completed the study and make recommendations to the trial Steering Committee. The unblinded statistician associated with the DSMB will make no contribution to the trial design or final analysis of the study. No interim analyses are planned. The Lawson Health Research Institute will be responsible for conducting periodic audits of the conduct of MPAC-CKD-1 (Micro-Particle Curcumin for the Treatment of Chronic Kidney Disease-1).

Dissemination Policy

We plan to disseminate the results of MPAC-CKD-1 (Micro-Particle Curcumin for the Treatment of Chronic Kidney Disease-1) through peer-reviewed publication. We will not employ professional writers and each author on the final article will have fulfilled the requirements set out by the International Committee of Medical Journal Editors.

Ethics Approval and Consent to Participate

We have obtained approval for the conduct of MPAC-CKD-1 (Micro-Particle Curcumin for the Treatment of Chronic Kidney Disease-1) from both the Western University research ethics board and the McMaster University research ethics board. Any modifications to the protocol that may impact the conduct of the study or affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will prompt a formal amendment. Revisions will be forwarded to each participating site with direction for submission to each respective research ethics board. The protocol and prespecified statistical analysis plan were approved by all authors and the data safety and monitoring board.

Consent to Participate is not required section for a Protocol publication type.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: No investigator or research personnel has a financial or other competing interest in MPAC-CKD-1. The study design and collection, management, analysis, and interpretation of the study data have not and will not involve the funders. The trial funders will have no role in the reporting of the results.
Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by grants from the Kidney Foundation of Canada (KFOC130029), and the Canadian Institute of Health Research (CIHR365629). Natural Factors Nutritional Products Ltd (Coquitlam, BC, Canada) supplied investigational product and matching placebo as in-kind support. Michael Walsh holds a New Investigator Award from the Canadian Institutes of Health Research. Amit X. Garg is supported by a Clinician Investigator Award from the Canadian Institutes of Health Research and the Adam Linton Chair in Kidney Health Analytics.

ORCID iD
Jessica M. Sontrop https://orcid.org/0000-0001-7784-2028

Supplemental Material
Supplemental material for this article is available online.

References
1. Collins AJ, Foley RN, Herzog C, et al. Excerpts from the US Renal Data System 2009 Annual Data Report. Am J Kidney Dis. 2010;55(suppl 1):S1-A7.
2. Kerr M, Bray B, Medcalf J, O’Donoghue DJ, Matthews B. Estimating the financial cost of chronic kidney disease to the NHS in England. Nephrol Dial Transplant. 2012;27(suppl 3):iii73-iii80.
3. Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int. 2003;63:225-232.
4. Remuzzi G, Benigni A, Remuzzi A. Mechanisms of progression and regression of renal lesions of chronic nephropathies and diabetes. J Clin Invest. 2006;116:288-296.
5. Ziyadeh FN, Wolf G. Pathogenesis of the podocytopathy and proteinuria in diabetic glomerulopathy. Curr Diabetes Rev. 2008;4:39-45.
6. Soetikno V, Watanabe K, Sari FR, et al. Curcumin attenuates diabetic nephropathy by inhibiting PKC-α and PKC-β1 activity in streptozotocin-induced type I diabetic rats. Mol Nutr Food Res. 2011;55:1655-1665.
7. Ghosh SS, Massey HD, Krieg R, et al. Curcumin ameliorates renal failure in 5/6 nephrectomized rats: role of inflammation. Am J Physiol Renal Physiol. 2009;296:F1146-F1157.
8. Ghosh SS, Krieg R, Massey HD, et al. Curcumin and enalapril ameliorate renal failure by antagonizing inflammation in 5/6 nephrectomized rats: role of phospholipase and cyclooxygenase. Am J Physiol Renal Physiol. 2012;302:F439-F454.
9. Sharma S, Kulkarni SK, Chopra K. Curcumin, the active principle of turmeric (Curcuma longa), ameliorates diabetic nephropathy in rats. Clin Exp Pharmacol Physiol. 2006;33:940-945.
10. Khajehdehi P, Pakfetrat M, Javidinia K, et al. Oral supplementation of turmeric attenuates proteinuria, transforming growth factor-β and interleukin-8 levels in patients with overt type 2 diabetic nephropathy: a randomized, double-blind and placebo-controlled study. Scand J Urol Nephrol. 2011;45:365-370.
11. Khajehdehi P, Zanjaniejad B, Aflaki E, et al. Oral supplementation of turmeric decreases proteinuria, hematuria, and systolic blood pressure in patients suffering from relapsing or refractory lupus nephritis: a randomized and placebo-controlled study. J Ren Nutr. 2012;22:50-57.
12. Shoskes D, Lapiere C, Cruz-Correa M, et al. Beneficial effects of the bioflavonoids curcumin and quercetin on early function in cadaveric renal transplantation: a randomized placebo-controlled trial. Transplantation. 2005;80:1556-1559.
13. Shoba G, Joy D, Joseph T, et al. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 1998;64:353-356.
14. Vareed SK, Kakarala M, Ruffin MT, et al. Pharmacokinetics of curcumin conjugate metabolites in healthy human subjects. Cancer Epidemiol Biomarkers Prev. 2008;17:1411-1417.
15. Shehzad A, Wahid F, Lee YS. Curcumin in cancer chemoprevention: molecular targets, pharmacokinetics, bioavailability, and clinical trials. Arch Pharm (Weinheim). 2010;343:489-499.
16. Sasaki H, Sunagawa Y, Takahashi K, et al. Innovative preparation of curcumin for improved oral bioavailability. Biol Pharm Bull. 2011;34:660-665.
17. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013:200-207.
18. Leung AA, Daskalopoulou SS, Dasgupta K, et al. Hypertension Canada’s 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. Can J Cardiol. 2017;33:557-576.
19. Tayyem RF, Heath DD, Al-Delaimy WK, et al. Curcumin content of turmeric and curry powders. Nutr Cancer. 2006;55:126-131.
20. Kwon Y. Estimation of curcumin intake in Korea based on the Korea National Health and Nutrition Examination Survey (2008-2012). Nutr Res Pract. 2014;8:589-594.
21. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-612.
22. Pari L, Murugan P. Antihyperlipidemic effect of curcumin and tetrahydrocurcumin in experimental type 2 diabetic rats. Ren Fail. 2007;29:881-889.
23. de Meloa ISV, Santosb Dos AF, Buenoc NB. Curcumin or combined curcuminoids are effective in lowering the fasting blood glucose concentrations of individuals with dysglycemia: systematic review and meta-analysis of randomized controlled trials. Pharmacol Res. 2018;128:137-144. doi:10.1016/j.phrs.2017.09.010.
24. Sahebkar A, Henrotin Y. Analgesic efficacy and safety of curcuminoids in clinical practice: a systematic review and meta-analysis of randomized controlled trials. Pain Med. 2016;17:1192-1202.
25. Ng QX, Koh SSH, Chan HW, Ho CYX. Clinical use of curcumin in depression: a meta-analysis. J Am Med Dir Assoc. 2017;18:503-508.
26. Clark WF, Sontrop JM, Huang S-H, et al. The chronic kidney disease Water Intake Trial (WIT): results from the pilot randomised controlled trial. BMJ Open. 2013;3:e003666.
27. Clark WF, Sontrop JM, Huang S-H, et al. Effect of coaching to increase water intake on kidney function decline in adults.
with chronic kidney disease: the CKD WIT randomized clinical trial. *JAMA.* 2018;319:1870-1879.
28. Sontrop JM, Garg AX, Li L, et al. Consecutive first-morning urine samples to measure change in the albumin-to-creatinine ratio: a pilot study of a home urine collection protocol. *Can J Kidney Health Dis.* 2016;3:3.
29. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med.* 1993;329:1456-1462.
30. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* 2001;345:851-860.
31. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* 2001;345:861-869.
32. Parving H-H, Persson F, Lewis JB, et al. Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med.* 2008;358:2433-2446.
33. Halbesma N, Kuiken D-S, Brantsma AH, et al. Macrophage-induced albuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. *J Am Soc Nephrol.* 2006;17:2582-2590.
34. Hunsicker LG, Adler S, Caggiula A, et al. Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. *Kidney Int.* 1997;51:1908-1919.
35. Huque MF. Validity of the Hochberg procedure revisited for clinical trial applications. *Stat Med.* 2016;35:5-20.
36. Bland JM, Altman DG. The use of transformation when comparing two means. *BMJ.* 1996;312:1153.
37. Little RJ, D’Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med.* 2012;367:1355-1360.
38. Nguyen T-L, Collins GS, Lamy A, et al. Simple randomization did not protect against bias in smaller trials. *J Clin Epidemiol.* 2017;84:105-113.
39. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med.* 2016;375:323-334.
40. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377:644-657.
41. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *JAMA.* 2016;315:164-174.
42. Gupta SC, Kim JH, Kannappan R, et al. Role of nuclear factor κB-mediated inflammatory pathways in cancer-related symptoms and their regulation by nutritional agents. *Exp Biol Med (Maywood).* 2011;236:658-671.
43. Yamaguchi M, Moore TW, Sun A, Snyder JP, Shoji M. Novel curcumin analogue UBS109 potently stimulates osteoblastogenesis and suppresses osteoclastogenesis: involvement in Smad activation and NF-κB inhibition. *Integr Biol (Camb).* 2012;4:905-913.
44. Qian J-J, Zhai X-G, Niu M-H, Zhou Q, Zhou YJ. [Curcumin inhibits iron overload-induced hepatocytic apoptosis and nuclear factor-κB activity]. *Zhonghua Yi Xue Za Zhi.* 2012;92:1997-2001.
45. Qiao Q, Jiang Y, Li G. Curcumin improves the antitumor effect of X-ray irradiation by blocking the NF-κB pathway: an in-vitro study of lymphoma. *Anticancer Drugs.* 2012;23:597-605.
46. Liu N, Tolbert E, Pang M, et al. Suramin inhibits renal fibrosis in chronic kidney disease. *J Am Soc Nephrol.* 2011;22:1064-1075.
47. Eddy AA. Molecular basis of renal fibrosis. *Pediatr Nephrol.* 2000;15:290-301.
48. Smith MR, Gangireddy SR, Narala VR, et al. Curcumin inhibits fibrosis-related effects in IPF fibroblasts and in mice following bleomycin-induced lung injury. *Am J Physiol Lung Cell Mol Physiol.* 2010;298:L16-L125.
49. Gaedeke J, Noble NA, Border WA. Curcumin blocks multiple sites of the TGF-beta signaling cascade in renal cells. *Kidney Int.* 2004;66:112-120.
50. Song K, Peng S, Sun Z, et al. Curcumin suppresses TGF-β signaling by inhibition of TGIF degradation in scleroderma fibroblasts. *Biochem Biophys Res Commun.* 2011;411:821-825.
51. Zheng S, Chen A. Disruption of transforming growth factor-beta signaling by curcumin induces gene expression of peroxisome proliferator-activated receptor-gamma in rat hepatic stellate cells. *Am J Physiol Gastrointest Liver Physiol.* 2007;292:G113-G123.
52. Hu Y, Liang H, Du Y, et al. Curcumin inhibits transforming growth factor-beta activity via inhibition of Smad signaling in HK-2 cells. *Am J Nephrol.* 2010;31:332-341.
Statistical Analysis Plan (SAP)

Micro-Particle Curcumin for the Treatment of Chronic Kidney Disease-1 (MPAC-CKD-1)
Signatures:

Principal Investigator/Author  Name: Matthew A. Weir
Signature: _______________________
Date: April 29, 2020

Author/Epidemiologist  Name: Jessica Sontrop
Signature: _______________________
Date: April 29, 2020

Author/Statistician  Name: Meaghan Cuerden
Signature: _______________________
Date: April 29, 2020
List of Abbreviations
ACE: Angiotensin converting enzyme
ACR: Albumin-to-creatinine ratio
ARB: Angiotensin receptor blocker
CI: Confidence interval
CKD: Chronic kidney disease
DSMB: Data safety monitoring board
eGFR: Estimated glomerular filtration rate
HR: Hazard ratio
MAR: Missing at random
RAAS: Renin-angiotensin-aldosterone
SD: Standard deviation

Study/trial acronyms
MPAC-CKD-1: Micro-PArticle Curcumin for the treatment of Chronic Kidney Disease-1
Table of Contents
1. Administrative Information
2. Introduction
   2.1 Background and rationale
   2.2 Objectives
3. Study Methods
   3.1 Trial design
   3.2 Randomization
   3.3 Sample size
   3.4 Framework
   3.5 Statistical interim analyses and stopping guidance
   3.6 Timing of the final analysis
   3.7 Timing of outcome assessments
4. Statistical Principles
   4.1 Confidence intervals and P values
   4.2 Adherence and protocol deviations
   4.3 Analysis populations
5. Trial Population
   5.1 Screening data
   5.2 Eligibility
   5.3 Recruitment
   5.4 Withdrawal/follow-up
   5.5 Baseline patient characteristics
6. Analysis
   6.1 Outcome definitions and analysis methods
   6.2 Missing data
   6.3 Additional analyses
   6.4 Harms
   6.5 Statistical software
   6.6 References
1. Administrative Information

Trial registration number: NCT 02369549

SAP version number: 1.0 dated April 13, 2020

Protocol version: Protocol Version 2.3 Dated December 22, 2016

Roles and responsibility:
Principal Investigator: Matthew A. Weir, MD, FRCPC, MSc 1,2,3,4
Co-Investigator: Amit X. Garg, MD, FRCPC, PhD 1,2,3,5
Epidemiologist: Jessica Sontrop, PhD 3
Statistician: Meaghan Cuerden, PhD 1
Trial Coordinator: Laura Chambers, BA 4,6

Contributors and Roles
Matthew A. Weir: Contributed to design of SAP
Jessica Sontrop: Contributed to design of SAP
Meaghan Cuerden: Contributed to design of SAP

Affiliations
1. London Health Sciences Centre, London, Ontario, Canada
2. Department of Medicine – Division of Nephrology, Schulich Medicine & Dentistry, Western University, London, Ontario, Canada
3. Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada
4. Lawson Health Research Institute, London, Ontario, Canada
5. Departments of Health Research Methods, Evidence, and Impact (HEI), McMaster University, Hamilton, Ontario, Canada
6. Kidney Clinical Research Unit, London, Ontario, Canada
2. Introduction

2.1 Background and rationale

Chronic kidney disease (CKD) is defined by an estimated glomerular filtration rate (eGFR) less than 60 mL/min per 1.73 m$^2$ or evidence of persistent kidney damage, such as excessive albuminuria. CKD is associated with significant morbidity and mortality but the most important complication of CKD is the progression to kidney failure (end-stage renal disease [ESRD]). Patients who progress to ESRD require dialysis or transplantation to survive. They experience numerous complications, have high mortality rates,$^1$ and their care is very expensive.$^2$ Therefore, preventing or slowing the progression from CKD to ESRD is an important clinical and research goal. Currently, few treatments have been proven to slow progression, and even when these therapies are appropriately applied, many patients still progress to ESRD.$^3$ This may be explained in part by inflammation and fibrosis, two processes that play a role in the progression of CKD,$^4,5$ but are not addressed by current therapies.

Curcumin, a component of the dietary spice turmeric, has proven anti-inflammatory and anti-fibrotic properties and has been shown to mitigate renal damage in multiple animal models of CKD.$^6-9$ The ability of curcumin to reduce albuminuria in humans is supported by two trials in patients with nephrotic-range proteinuria.$^{10-12}$ However, these trials were small and patients were treated with turmeric, of which curcumin is only a small component. Furthermore, curcumin in its traditional form has very poor bioavailability.$^{13-15}$ To increase patients’ exposure to curcumin, we chose to study a micro-particle formulation that is 27 times more bioavailable.$^{16}$ Curcumin use has been associated with improved glycemic control in animal models,$^{17}$ and human studies.$^{18}$

MPAC-CKD-1 is a double-blind, placebo-controlled randomized trial, where patients are followed for 6-months after randomization. The primary goal of the trial is to assess the effect of micro-particle curcumin (versus placebo) on two important biomarkers of CKD progression: albuminuria and eGFR. Positive effects in either of these markers will justify a larger, international trial to determine whether micro-particle curcumin versus placebo decreases the risk of ESRD in patients with CKD.

2.2 Objectives

Our primary objective is to assess the between-group difference in two outcomes examined separately: urinary albumin-to-creatinine ratio (6-month post-randomization value) and change in eGFR from pre-randomization to 6-months post-randomization.

Our secondary objective is to assess: i) the between-group difference in health related quality of life (as assessed by a 6-month change in the RAND version of the 36-Item Short Form Health Survey [SF-36]), ii) the between-group difference in glycemic control (as assessed by a 6-month change in glycated hemoglobin among patients with diabetes mellitus; diabetes mellitus was a stratification variable in the randomization), iii) the risk of a composite outcome of progressive CKD, ESRD or death with micro-particle curcumin versus placebo, and iv) the between-group difference in measured serum levels of curcumin and its major metabolites (to be done on measurements taken 3-months after randomization in the first 30 participants; being done to assess curcumin bioavailability)$^{14,16}$

We will also conduct a pre-specified exploratory subgroup analysis of the primary outcomes based on a higher or lower estimated risk of future kidney failure (based on the kidney failure risk equation$^{19}$).
3. Study Methods

3.1 Trial design

MPAC-CKD-1 is a parallel group, double-blind, placebo-controlled randomized trial. Participants were randomly assigned to receive either microparticle curcumin or matching placebo in a 1:1 ratio. Microparticle curcumin was administered at 90 mg per day (three 30 mg capsules once daily) for 6 months. The dose remained constant over the study period.

3.2 Randomization

Balanced block randomization was conducted using a computerized algorithm with variable block sizes; treatment allocation was stratified by site (3 sites in London, 1 site in Hamilton) and by the presence or absence of baseline diabetes mellitus. After providing written informed consent, patients were allocated randomly by means of a 24-hour online computerized system to maintain allocation concealment. Participants, investigators, and all research staff are unaware of the treatment allocation. Unblinding could have occurred in the setting of a severe adverse reaction in which the treating physician believed the investigational product may have had a role in the patient’s condition or treatment. Unblinding events will be summarized by group.

3.3 Sample size

Most physicians would view a 15% to 25% reduction in albuminuria as evidence of a promising treatment effect. Such was the case for angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), which showed a reduction in albuminuria of 15% to 50% and were later proven to reduce the risk of mortality and ESRD.\textsuperscript{20-23}

Heerspink et al.\textsuperscript{24} conducted a meta-analysis of randomized controlled trials with different types of interventions, including renin-angiotensin-aldosterone (RAAS) inhibitor versus control, and RAAS inhibitor versus calcium-channel blocker. The overall between-group difference in change in log-transformed urine albumin-to-creatinine ratio after 6-months of follow-up was reported as a geometric mean ratio and was estimated using patient-level data. Across all treatment interventions, the estimate of the geometric mean ratio was 0.78, 95% confidence interval (CI) 0.74 to 0.82 (i.e. a lowering of urinary albumin-to-creatinine ratio across treatment groups). Within the same trials, over a median follow-up time of 3.4 years, the active treatment resulted in a lowering of the hazard of the composite progressive CKD endpoint defined by ESRD (chronic dialysis or transplant), doubling of serum creatinine or eGFR < 15 mL/min per 1.73 m\textsuperscript{2} (hazard ratio [HR] 0.73, 95% CI 0.67 to 0.81). The authors estimated that a 30% decrease in geometric mean ratio of 6-month urinary albumin-to-creatinine ratio is associated with an average 27% decrease in the hazard for the clinical outcome. Inker et al.\textsuperscript{25} conducted a similar meta-analysis of treatment effects in randomized controlled trials to investigate between-group difference in change in eGFR over time as a surrogate endpoint for kidney disease progression. The authors found that the overall mean treatment effect on the total slope over 3 years was 0.45 mL/min per 1.73 m\textsuperscript{2}, 95% CI 0.19 to 0.72, comparing treated patients to control arm patients. The active treatment led to a HR of the same composite progressive CKD endpoint of 0.76, 95% CI 0.69 to 0.84. The authors estimate that each 0.75 mL/min per 1.73m\textsuperscript{2} per year greater treatment effect on the total eGFR slope was associated with an average 27% lower hazard for the clinical endpoint.

In our preliminary work on urinary albumin-to-creatinine ratio testing, we found patients eligible for MPAC-CKD-1 had a mean initial urinary albumin-to-creatinine ratio of 128.3 mg/mmol.\textsuperscript{26} Over 3 months, we observed a mean increase in the urinary albumin-to-creatinine ratio of 30.7 mg/mmol and found the standard deviation of the change to be 69.2 mg/mmol. Enrolling a total of 518 patients and
accounting for 5% loss to follow-up allows for 82% power ($\alpha = 0.025$) to detect a geometric mean ratio of 0.75, assuming a standard deviation of the 6-month log-transformed albumin-to-creatinine ratio of 1.0.\(^{27}\)

For the between-group difference in change in eGFR (6-month eGFR minus pre-randomization eGFR), we will have 81% power ($\alpha = 0.025$) to exclude a difference of 1.65 mL/min per 1.73 m\(^2\) between treatment and control groups (using a standard deviation of the change of 5.8 mL/min per 1.73 m\(^2\)). In general, the average decline in eGFR in albuminuric CKD patients is 2 to 4 mL/min per 1.73 m\(^2\) per year (with a standard deviation of 3-4 mL/min per 1.73 m\(^2\) per year).\(^{28,29}\) The standard deviations used in these sample size calculations are based on overall standard deviations observed in the MPAC-CKD-1 study.

3.4 Framework

All comparisons will be presented in a superiority testing framework.

3.5 Statistical interim analyses and stopping guidance

An interim report was created when 50% of patients were randomized and had completed the last scheduled visit. An independent statistician, who was blinded to the treatment allocation, created the interim report. The statistician reported to an independent Data Safety Monitoring Board (DSMB). The DSMB was blinded to all data (stratified groups were denoted as group “A” and group “B”) and discussed the results of the interim analysis with the statistician. No between-group tests were conducted for the two primary outcomes or for any other endpoints. The DSMB also reviewed safety events. The DSMB recommended the trial continue to completion and decided not to unblind itself to the interim data.

3.6 Timing of the final analysis

The final analysis will occur within 6 months of completing data collection; the final analysis is planned for mid-2020.

3.7 Timing of outcome assessments

Telephone calls to participants are made at 1 week, 1 month, 2 months, 4 months and 5 months post-randomization. After a baseline set of measurements, urine samples, blood samples, and SF-36 form completion occurs at the 3-month and 6-month visits. The study drug is stopped immediately after the 6-month follow-up visit; a final telephone call is made to participants 7-months post-randomization.
4. Statistical Principles

4.1 Confidence intervals and P values

The overall type I error rate will be fixed at 0.05. The Hochberg procedure will be used to test each of the two-sided hypothesis tests for the two primary outcomes. The largest of the two P values will be compared to $\alpha = 0.05$, and if this test is non-significant, the smaller P value will be compared to $\alpha/2 = 0.025$. If the largest P value is < 0.05, both hypothesis tests will be rejected. If both of the two primary outcomes are tested at the 0.05 significance level, 95% CIs will be reported; if either of the primary outcomes are tested at the 0.025 significance level, 97.5% CIs will be reported for both tests.

All secondary analyses will be considered exploratory in nature and P values will not be reported; 95% CIs will be reported without adjustment for multiple testing.

4.2 Adherence and protocol deviations

Protocol compliance was assessed through pill counts and interviews at each follow-up visit. Protocol deviation is defined as missing taking the study medication over 7 or more days during any 4-week period. Patients who miss taking the medication over 7 or more days during any 4-week period will meet with an investigator to discuss ways of improving adherence. We will report the number and percentage of participants who experience at least one protocol deviation, overall and by treatment group. We will report the median (25th and 75th percentiles) number of doses missed over the entire study period, overall and by group.

Study treatment discontinuation is defined as missing study medication for ≥ 4 weeks consecutively. We will report the number and percentage of participants who discontinue the study, overall and by group.

4.3 Analysis populations

We will conduct all primary analyses according to the intention-to-treat (ITT) principle. We will conduct an exploratory per-protocol analysis for each of the two primary outcomes consisting of patients who were adherent to their randomly assigned treatment, as defined by taking ≥ 80% of pills given during the first three months of follow-up (or were adherent until they died or developed ESRD if this occurred within the first three months).
5. Trial Population

5.1 Screening data

Patient characteristics were not recorded for patients who were assessed for eligibility but were either (i) not eligible or (ii) not interested in participating.

5.2 Eligibility

Patients with an eGFR between 15 and 60 mL/min per 1.73 m$^2$ and overt albuminuria, defined by either a 24-hour urine collection with a minimum of 300 mg of protein or a urinary albumin-to-creatinine ratio equivalent to a daily excretion of albumin of at least 300 mg, were recruited. Patients with conditions that may potentially be exacerbated by the use of micro-particle curcumin (active peptic ulcer disease, hepatobiliary disease, history of significant bleeding) or who take medications that may interact with micro-particle curcumin were excluded (Table 1).

5.3 Recruitment

The participant recruitment and randomization flow diagram will follow CONSORT recommendations. We will report the number of participants approached to participate in MPAC-CKD-1, as well as the number of participants who: (i) declined to participate, (ii) were approached but were found to be ineligible, (iii) were randomized, (iv) received the allocated intervention, (v) were lost to follow-up or discontinued the intervention, (vi) were included in the final analysis.

5.4 Withdrawal/follow-up

Participants who stop taking the study drug, but do not withdraw consent to participate in the study, will continue with the study’s scheduled telephone visits and may replace remaining in-person visits with telephone visits. Participants wishing to withdraw consent will be asked to complete the closing telephone visit (scheduled for 4 weeks after study drug completion) 4 weeks after withdrawal of consent. The number and percentage of participants who withdraw from the study will be reported overall and by group. Reasons for study withdrawal will be presented in a supplementary document.

5.5 Baseline patient characteristics

Table 2 contains a summary of baseline (pre-randomization) characteristics to be summarized by group. Continuous baseline characteristics will be summarized as mean (standard deviation [SD]) and categorical baseline characteristics will be summarized as number (percent).
6. Analysis

See Supplemental Table 1 for information on changes made to the analysis section of the MPAC-CKD-1 study protocol published in The Canadian Journal of Kidney Health and Disease. These changes were made without knowledge of the trial results.

6.1 Outcome definitions and analysis methods

Two primary outcomes

We will assess two outcomes: the between-group difference in 6-month urinary albumin-to-creatinine ratio (log-transformed, measured in mg/mmol), and the 6-month change in eGFR (6-months post-randomization minus pre-randomization, measured in mL/min per 1.73m²). Placebo will serve as the referent group in all analyses.

Albuminuria: Albuminuria will be measured using urinary albumin-to-creatinine ratio from first morning urine samples. At each visit (pre-randomization, and 3- and 6-months post-randomization), urinary albumin-to-creatinine ratio is measured on two consecutive days and the average of the two values will be computed. The average of the two values will be log-transformed using the natural logarithm. A summary of the pre-treatment, 3-month and 6-month urinary albumin-to-creatinine ratio measurements will be provided. The geometric mean ratio of 6-month urinary albumin-to-creatinine ratio will be estimated using linear regression, where the outcome is the log-transformed average of two 6-month follow-up visit urinary albumin-to-creatinine ratio measurements minus log-transformed average of two pre-treatment urinary albumin-to-creatinine ratio measurements, adjusting for a treatment indicator variable and the log-transformed average of two baseline urinary albumin-to-creatinine ratio measurements. The 95% or 97.5% CI for the geometric mean ratio will be presented.

eGFR: eGFR will be calculated using the CKD-EPI formula, which includes patient age, sex, race (black vs. other), and the serum creatinine concentration. We will summarize the pre-randomization, 3-month and 6-month eGFR measurements by group. We will estimate the between-group difference in change in eGFR (6-month eGFR minus pre-randomization eGFR), expressed in mL/min per 1.73m², using linear regression. The outcome is the change in eGFR (6-month value minus pre-randomization value) and the treatment indicator variable will be included as a covariate. The 95% or 97.5% CI for the between-group difference in change in eGFR will be presented.

Secondary outcomes

Health-related quality of life: We will summarize health-related quality of life scores determined by the RAND version of the 36-Item Short Form Health Survey (SF-36) administered pre-randomization and at 3-months and 6-months post-randomization. The physical composite summary (PCS) score and mental composite summary (MCS) score of the SF-36 will be examined separately. The between-group difference in change in each composite score, 6-month value minus pre-randomization value, will be reported with 95% CIs. Beyond preservation of kidney function are several other potential mechanisms by which curcumin may benefit quality of life, including potential benefits on depression and chronic pain.

Glycemic control: We will summarize the percentage of glycated hemoglobin pre-randomization and at 3-months and 6-months post-randomization. We will present the between-group difference in change in percentage of glycated hemoglobin (6-month value minus pre-randomization value) among patients with diabetes mellitus (diabetes mellitus was a stratification variable in the randomization), with the 95% CI.
Progressive CKD, ESRD and death: We will report on the outcome of progressive CKD, ESRD, and death, first as a composite outcome, and then as separate components. We will define ESRD as an eGFR <15 mL/min/1.73 m² or the initiation of renal replacement therapy, which includes chronic dialysis or transplantation; progressive CKD will be defined as an eGFR loss of ≥ 30% (anytime during follow-up from the pre-randomization baseline value) or ESRD. We expect less than 10% of participants will experience these outcomes by 6 months. Our focus is to document any trends to inform the expected event rate for future studies. Each outcome (progressive CKD, ESRD and death) will be summarized separately as number (percentage) of patients with the event by group. The HR of progressive CKD (as its own outcome) will be estimated using Cox proportional hazards regression, treating death as a competing event. The same approach will be used for the outcome of ESRD. Each estimate will be reported with 95% CIs.

Serum curcumin levels: To confirm our micro-particle curcumin was bioavailable, and to strengthen any relationship between micro-particle curcumin and any outcomes we identify, serum levels of curcumin and its major metabolites were measured in the first 30 participants 3 months after randomization (including patients taking micro-particle curcumin and those taking placebo). Serum curcumin and its major metabolites will be summarized in the first 30 participants randomized, by group. The between-group difference in average serum curcumin levels measured 3-months post-randomization will be reported with the 95% CI.

Pre-specified subgroup analysis
We will conduct an exploratory subgroup analysis based on a higher or lower estimated risk of kidney failure, using the kidney failure risk equation. Participants with a 2-year risk of ESRD less than 10% will be classified as lower risk, and patients with a risk of 10% or more will be classified as higher risk. For both primary outcomes, separate regression models with an interaction term between randomization group and the kidney failure risk category indicator variable will be used. The 6-month albumin-to-creatinine ratio geometric mean ratio will be reported for each kidney failure risk equation group, and the difference in change in eGFR will be reported for each kidney failure risk group, along with 95% CIs.

Missing data for reasons other than death will be handled using model-based multiple imputation methods (as the primary method to handle missing data in all analyses). Additional analyses will be performed to confirm that conclusions are not sensitive to assumptions about the missing-data mechanism. In the primary analyses, outcomes that are missing due to death will not be imputed (expected in less than 5% of patients). In sensitivity analyses, to account for missing values due to death we will (i) use multiple imputation to impute missing outcomes; (ii) use single imputation where a missing 6-month albumin-to-creatinine ratio will be imputed as a doubling of the baseline albumin-to-creatinine ratio value, and 6-month eGFR will be imputed as half of the pre-randomization eGFR. Pre-randomization data, the treatment variable, stratification variables, and data collected at both the 3-month and 6-month visits will be included in the multiple imputation models. For patients missing both urinary albumin-to-creatinine ratio measurements at a particular visit, one urinary albumin-to-creatinine ratio will be imputed as the average value; urinary albumin-to-creatinine ratio will be imputed on the log scale. If a patient is missing one of the two urinary albumin-to-creatinine ratio measurements at a particular visit, the single observed value will be taken as the average urinary albumin-to-creatinine ratio for that visit and no imputation will occur. Estimates from each complete dataset will be combined using standard methods. The imputation model will allow for an interaction effect between the treatment variable and the kidney failure risk equation indicator variable.

For all primary and secondary outcomes, the pre-randomization, 3-month and 6-month measurements will be summarized by group as mean (standard deviation) and median (25th and 75th percentiles) or number and percentage, depending on whether the variable is continuous or categorical.
Randomization reliably removes random differences between treatment groups when at least 1000 participants are included. With the size of our sample, it is possible that imbalances may arise between the treatment groups on important characteristics that may influence outcomes. In sensitivity analyses, we will repeat the two primary analyses while (i) accounting for randomization strata (centre and pre-randomization diabetes); (ii) accounting for randomization strata and adjusting for variables associated with disease progression including age, sex, tobacco use, blood pressure, baseline use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and baseline use of aldosterone antagonists. We do not anticipate that accounting for randomization strata and/or adjustment for pre-randomization variables will change the results in any meaningful way.

### 6.2 Missing data

The number and percentage of participants with missing outcome data (all primary and secondary outcomes) at the 3-month and 6-month visits will be reported for each group. See Section 6.1 for details on multiple imputation for missing values. We will assume that data are missing at random (MAR).

### 6.3 Additional analyses

No additional analyses are planned.

### 6.4 Harms

**Study medication discontinuation**

We will report the number and percentage of patients who discontinue the study medication by group, as study medication discontinuation can suggest that the drug is poorly tolerated.

In addition, we will report the number and percentage of participants who experience the following side effects which are assessed using standardized case report forms at the 3-month and 6-month follow-up visits.

**Minor side-effects**

In rare cases, curcumin has been reported to cause minor nausea, headache, diarrhea, yellow stool, temporary giddiness, localized swelling of the skin (contact dermatitis), or hives (urticaria). The number and percentage of patients who experience each of these side effects will be reported by treatment group, and the number of minor side effects experienced by each patient will be summarized by group. For each minor side-effect, a Chi-squared test will be used to test whether the percentage of patients experiencing the minor side-effect is equal between groups; P values will be tested at the 0.05 significance level.

**Bleeding**

In the 1990s, two studies described curcumin’s *in vitro* activity against platelet function. Further *in vitro* work has since identified curcumin’s ability to inhibit platelet activation, which could increase the risk of bleeding. However, when applied in animal models, curcumin appears to have no effect on clinically relevant bleeding, and in a recent study of oral curcumin loading immediately prior to abdominal aortic aneurysm repair, no significant risk of bleeding was identified. The number and percentage of patients experiencing a bleeding event during the course of the study will be reported by treatment group. A Chi-squared test will be used to test whether the percentage of patients experiencing at least one bleeding event is equal between groups; P values will be tested at the 0.05 significance level.

**Hypoglycemia**

Curcumin is a potent inhibitor of CYP2C9, which could increase the pharmacologic effects of some antidiabetic medications such as sulfonylureas. Although curcumin has been studied extensively in the
setting of diabetes and found to have a low risk of hypoglycemia,\textsuperscript{56} we will collect data on this potential adverse event and report the risk by treatment group. A Chi-squared test will be used to test whether the percentage of patients with diabetes pre-randomization experiencing at least one hypoglycemic event in follow-up is equal between groups; P values will be tested at the 0.05 significance level.\textsuperscript{41}

\textit{6.5 Statistical software}

SAS software version 9.4 will be used for all analyses.
6.6 References

1. Collins AJ, Foley RN, Herzog C, et al. Excerpts from the US Renal Data System 2009 Annual Data Report. *Am J Kidney Dis.* 2010;55(suppl 1):S1-A7.
2. Kerr M, Bray B, Medcalf J, O’Donoghue DJ, Matthews B. Estimating the financial cost of chronic kidney disease to the NHS in England. *Nephrol Dial Transplant.* 2012;27(suppl 3):iii73-iii80.
3. Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int.* 2003;63:225-232.
4. Remuzzi G, Benigni A, Remuzzi A. Mechanisms of progression and regression of renal lesions of chronic nephropathies and diabetes. *J Clin Invest.* 2006;116:288-296.
5. Ziyadeh FN, Wolf G. Pathogenesis of the podocytopathy and proteinuria in diabetic glomerulopathy. *Curr Diabetes Rev.* 2008;4:39-45.
6. Soetikno V, Watanabe K, Sari FR, et al. Curcumin attenuates diabetic nephropathy by inhibiting PKC-α and PKC-β1 activity in streptozotocin-induced type I diabetic rats. *Mol Nutr Food Res.* 2011;55:1655-1665.
7. Ghosh SS, Massey HD, Krieg R, et al. Curcumin ameliorates renal failure in 5/6 nephrectomized rats: role of inflammation. *Am J Physiol Renal Physiol.* 2009;296:F1146-F1157.
8. Ghosh SS, Krieg R, Massey HD, et al. Curcumin and enalapril ameliorate renal failure by antagonizing inflammation in 5/6 nephrectomized rats: role of phospholipase and cyclooxygenase. *Am J Physiol Renal Physiol.* 2012;302:F439-F454.
9. Sharma S, Kulkarni SK, Chopra K. Curcumin, the active principle of turmeric (Curcuma longa), ameliorates diabetic nephropathy in rats. *Clin Exp Pharmacol Physiol.* 2006;33:940-945.
10. Khajehehdehi P, Pakfetrat M, Javidnia K, et al. Oral supplementation of turmeric attenuates proteinuria, transforming growth factor-β and interleukin-8 levels in patients with overt type 2 diabetic nephropathy: a randomized, double-blind and placebo-controlled study. *Scand J Urol Nephrol.* 2011;45:365-370.
11. Khajehehdehi P, Zanjaneinjebad B, Aflaki E, et al. Oral supplementation of turmeric decreases proteinuria, hematuria, and systolic blood pressure in patients suffering from relapsing or refractory lupus nephritis: a randomized and placebo-controlled study. *J Ren Nutr.* 2012;22:50-57.
12. Shoskes D, Lapierre C, Cruz-Correa M, et al. Beneficial effects of the bioflavonoids curcumin and quercetin on early function in cadaveric renal transplantation: a randomized placebo controlled trial. *Transplantation.* 2005;80:1556-1559.
13. Shoba G, Joy D, Joseph T, et al. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med.* 1998;64:353-356.
14. Vareed SK, Kakarala M, Ruffin MT, et al. Pharmacokinetics of curcumin conjugate metabolites in healthy human subjects. *Cancer Epidemiol Biomarkers Prev.* 2008;17:1411-1417.
15. Shehzad A, Wahid F, Lee YS. Curcumin in cancer chemoprevention: molecular targets, pharmacokinetics, bioavailability, and clinical trials. *Arch Pharm* (Weinheim). 2010;343:489-499.
16. Sasaki H, Sunagawa Y, Takahashi K, et al. Innovative preparation of curcumin for improved oral bioavailability. *Biol Pharm Bull.* 2011;34:660-665.
17. Pari L, Murugan P. Antihyperlipidemic effect of curcumin and tetrahydrocurcumin in experimental type 2 diabetic rats. *Ren Fail.* 2007;29:881-889.
18. de Meloa ISV, Santosb Dos AF, Buenoc NB. Curcumin or combined curcuminoids are effective in lowering the fasting blood glucose concentrations of individuals with dysglycemia: systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res.* 2018;128:137-144.
19. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *JAMA.* 2016;315:164-174.
20. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med*. 1993;329:1456-1462.
21. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851-860.
22. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861-869.
23. Parving H-H, Persson F, Lewis JB, et al. Alikiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med*. 2008;358:2433-2446.
24. Heerspink HJL, Greene T, Tighiouart H, et al. Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials. *Lancet Diabetes Endocrinol*. 2019;7:128-39.
25. Inker LA, Heerspink HJL, Tighiouart H, et al. GFR slope as a surrogate end point for kidney disease progression in clinical trials: a meta-analysis of treatment effects in randomized controlled trials. *J Am Soc Nephrol*. 2019;30:1735-1745.
26. Sontrop JM, Garg AX, Li L, et al. Consecutive first-morning urine samples to measure change in the albumin-to-creatinine ratio: a pilot study of a home urine collection protocol. *Can J Kidney Health Dis*. 2016;3:3.
27. Wolfe R, Carlin JB. Sample-size calculation for a log-transformed outcome measure. *Control Clin Trials*. 1999;20:547-554.
28. Halbesma N, Kuiken D-S, Brantsma AH, et al. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. *J Am Soc Nephrol*. 2006;17:2582-2590.
29. Hunsicker LG, Adler S, Caggiula A, et al. Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. *Kidney Int*. 1997;51:1908-1919.
30. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*. 1988;75(4):800-802.
31. http://www.consort-statement.org/consort-statement/flow-diagram (date of last access: April 12, 2020)
32. Weir MA, Walsh M, Cuerden MS, et al. Micro-particle curcumin for the treatment of chronic kidney disease-I: study protocol for a multicenter clinical trial. *Can J Kidney Health Dis*. 2018;5:1-9.
33. Bland JM, Altman DG. The use of transformation when comparing two means. *BMJ*. 1996;312:1153.
34. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604-612.
35. Sahebkar A, Henrotin Y. Analgesic efficacy and safety of curcuminoids in clinical practice: a systematic review and metaanalysis of randomized controlled trials. *Pain Med*. 2016;17:1192-1202.
36. Ng QX, Koh SSH, Chan HW, Ho CYX. Clinical use of curcumin in depression: a meta-analysis. *J Am Med Dir Assoc*. 2017;18:503-508.
37. Little RJ, D’Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med*. 2012;367:1355-1360.
38. Rubin DB. Multiple imputation after 18+ years. *J Am Stat Assoc*. 1996;91(434):473-489.
39. Slade E, Naylor MG. A fair comparison of tree-based and parametric methods in multiple imputation by chained equations. *Stat Med*. 2020;39:1156-1166.
40. Nguyen T-L, Collins GS, Lamy A, et al. Simple randomization did not protect against bias in smaller trials. *J Clin Epidemiol*. 2017;84:105-113.
41. https://www.nejm.org/author-center/new-manuscripts (date of last access: April 12, 2020)
42. Shah BH, Nawaz Z, Pertani SA, et al. Inhibitory effect of curcumin, a food spice from turmeric, on platelet-activating factor- and arachidonic acid-mediated platelet aggregation through
inhibition of thromboxane formation and Ca2+ signaling. Biochem Pharmacol 1999;58(7):1167–72.

43. Srivastava KC, Bordia A, Verma SK. Curcumin, a major component of food spice turmeric (Curcuma longa) inhibits aggregation and alters eicosanoid metabolism in human blood platelets. Prostaglandins Leukot Essent Fatty Acids 1995;52(4):223–7.

44. Pan CJ, Shao ZY, Tang JJ, Wang J, Huang N. In vitro studies of platelet adhesion, activation, and protein adsorption on curcumin-eluting biodegradable stent materials. J Biomed Mater Res A 2007;82(3):740–6.

45. Zhang L, Gu Z-L, Qin Z-H, Liang Z-Q. Effect of curcumin on the adhesion of platelets to brain microvascular endothelial cells in vitro. Acta Pharmacol Sin 2008;29(7):800–7.

46. Kim D-C, Ku S-K, Bae J-S. Anticoagulant activities of curcumin and its derivative. BMB Rep 2012;45(4):221–6.

47. Mayanglambam A, Dangelmaier CA, Thomas D, et al. Curcumin inhibits GPVI-mediated platelet activation by interfering with the kinase activity of Syk and the subsequent activation of PLCgamma2. Platelets 2010;21(3):211–20.

48. Prakash P, Misra A, Surin WR, et al. Anti-platelet effects of Curcuma oil in experimental models of myocardial ischemia-reperfusion and thrombosis. Thromb Res 2011;127(2):111–8.

49. Wakade C, King MD, Laird MD, Alleyne CH, Dhandapani KM. Curcumin attenuates vascular inflammation and cerebral vasospasm after subarachnoid hemorrhage in mice. Antioxid Redox Signal 2009;11(1):35–45.

50. Yang Z, Zhao T, Zou Y, Zhang JH, Feng H. Curcumin inhibits microglia inflammation and confers neuroprotection in intracerebral hemorrhage. Immunol Lett 2014;160(1):89–95.

51. King MD, McCracken DJ, Wade FM, et al. Attenuation of hematoma size and neurological injury with curcumin following intracerebral hemorrhage in mice. J Neurosurg 2011;115(1):116–23.

52. Kuo C-P, Lu C-H, Wen L-L, et al. Neuroprotective effect of curcumin in an experimental rat model of subarachnoid hemorrhage. Anesthesiology 2011;115(6):1229–38.

53. Sun Y, Dai M, Wang Y, et al. Neuroprotection and sensorimotor functional improvement by curcumin after intracerebral hemorrhage in mice. J Neurotrauma 2011;28(12):2513–21.

54. Garg AX, Devereaux PJ, Hill A, et al. Oral curcumin in elective abdominal aortic aneurysm repair: a multicentre randomized controlled trial. Can Med Assoc J. 2018;190(43):E1273-E1280.

55. Bamba Y, Yun YS, Kunugi A, Inoue H. Compounds isolated from Curcuma aromatica Salisb. inhibit human P450 enzymes. J Nat Med 2011;65(3-4):583–7.

56. Zhang D-W, Fu M, Gao S-H, Liu J-L. Curcumin and Diabetes: A Systematic Review. Evidence-Based Complementary and Alternative Medicine 2013;2013(2):1–16.
Table 1. Inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|--------------------|--------------------|
| 18 years of age and older | Life expectancy < 1 year (Operational definition: presence of a terminal illness with a poor prognosis resulting in a documented expected life span of less than 1 year; advanced chronic kidney disease (stage IV or stage V) with a clear plan to forgo renal replacement therapy) |
| eGFR between 15 and 60 mL/min per 1.73 m² (calculated on a steady-state serum creatinine level using the CKD-EPI formula) | Known allergy to turmeric or its derivatives (ginger, curry, cumin, or cardamom); known allergy to ingredients of the study product or placebo [microcrystalline cellulose, vegetarian capsule (carbohydrate gum [cellulose], purified water), vegetable grade magnesium stearate (lubricant), silica] |
| Albuminuria, defined by the most recent measurement within the prior 3 months showing either: (a) 24-hour urine collection with a minimum of 300 mg of protein, or (b) urinary ACR equivalent to a daily excretion of albumin of at least 300 mg | Known allergy to ingredients of the study product or placebo [microcrystalline cellulose, vegetarian capsule (carbohydrate gum [cellulose], purified water), vegetable grade magnesium stearate (lubricant), silica] |
| If receiving an ACE inhibitor or ARB, the dosage must be stable for 2 weeks prior to screening. Patients not taking an ACE inhibitor or ARB must have a documented medical contraindication (e.g. hyperkalemia, hypotension) | Pregnant or breastfeeding (Operational definition: Women of child bearing potential are those who are not either surgically sterile (bilateral tubal ligation, hysterectomy, bilateral salpingo-oophorectomy) or not postmenopausal for at least 1 year) |
| For those with diabetes mellitus, willing to measure and record blood glucose concentrations | Plans for transplantation during the study period (Operational definition: Patients who have completed a transplant recipient work-up or who are active on the renal transplant list) |
| Willing and able to give written informed consent for participation and provide consent for access to medical data according to local data protection laws and regulations | Receipt of hemodialysis or peritoneal dialysis in the past 3 months (Operational definition: Active peptic ulcer disease includes patients who are: i. Currently receiving H. pylori eradication therapy or have received it in the past 30 days (H. pylori eradication therapy is combination therapy with a proton pump inhibitor [lansoprazole 30 mg twice daily, omeprazole 20 mg twice daily, pantoprazole 40 mg twice daily, rabeprazole 20 mg twice daily, or esomeprazole 40 mg once daily], amoxicillin [1 g twice daily], and clarithromycin [500 mg twice daily] for 7 to 14 days) ii. Awaiting upper endoscopy) |

Active peptic ulcer disease |
| Condition                                                                 | Operational definition                                                                 |
|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| Hepatobiliary disease in the past 4 weeks (biliary obstruction, cholecystis) | i. Patients with biliary obstruction includes those with a diagnosis of obstruction  
ii. Patients with cholecystitis include those with diagnosed cholecystitis and those with suspected cholecystitis (right upper quadrant abdominal pain that may radiate to the back or right shoulder that lasts four to six hours and may be exacerbated by ingestion of fatty foods) |
| Evidence of acute kidney injury (>50% increase in serum creatinine in the past 30 days) | Operational definition: gastrointestinal or retroperitoneal bleed requiring transfusion, or any intracranial hemorrhage in the last 6 months |
| History of significant bleeding                                             |                                                                                         |
| Ongoing use of warfarin                                                   |                                                                                         |
| Ongoing chemotherapy treatment with cyclophosphamide, camptothecin, mechlorethamine or doxorubicin |                                                                                         |
| Ongoing use of anti-psychotic including haloperidol, aripiprazole, risperidone, ziprasidone, pimozide, and quetiapine |                                                                                         |
| Previous participation in MPAC-CKD-1                                      |                                                                                         |
| Current participation in another investigational medication trial          |                                                                                         |

Abbreviations: ACE angiotensin converting enzyme; ACR albumin-to-creatinine ratio; ARB angiotensin receptor blocker; CKD chronic kidney disease
Table 2. Pre-randomization/pre-treatment participant characteristics

| Participant characteristic                      | Summary measure                  |
|------------------------------------------------|----------------------------------|
| Age at recruitment, years                       | mean (SD)                        |
| Male                                           | n (%)                            |
| Height, cm                                      | mean (SD)                        |
| Weight, kg                                      | mean (SD)                        |
| Body mass index, kg/m²                          | mean (SD)                        |
| Body mass index categories, kg/m²               | n (%)                            |
| < 25 kg/m²                                      |                                  |
| 25-29 kg/m²                                     |                                  |
| 30-34 kg/m²                                     |                                  |
| ≥ 35 kg/m²                                      |                                  |
| Systolic blood pressure, mmHg                   | mean (SD)                        |
| Diastolic blood pressure, mmHg                  | mean (SD)                        |
| Serum creatinine, μmol/L                        | mean (SD)                        |
| eGFR, mL/min per 1.73m²                        | mean (SD)                        |
| eGFR categories, mL/min per 1.73m²             | n (%)                            |
| 45-60                                          |                                  |
| 30-44                                          |                                  |
| < 30                                           |                                  |
| Urinary albumin to creatinine ratio, mg/mmol    | mean (SD)                        |
| Race/ethnicity                                  | n (%)                            |
| White/Caucasian                                 |                                  |
| Black/African American/African Canadian         |                                  |
| Hispanic/Latino                                 |                                  |
| Asian (Far East, Southeast Asia, Indian Subcontinent) |                      |
| Middle East                                     |                                  |
| Aboriginal/Native Persons/American Indian      |                                  |
| Other                                           |                                  |
| Diabetes                                        | n (%)                            |
| HbA1c                                           | mean (SD)                        |
| Insulin use                                     | n (%)                            |
| Oral hypoglycemic                               |                                  |
| Insulin or oral hypoglycemic                    |                                  |
| History of smoking                              | n (%)                            |
| Current                                         |                                  |
| Remote b                                        |                                  |
| No                                              |                                  |
| Primary cause of CKD                            | n (%)                            |
| Diabetic nephropathy                            |                                  |
| Glomerulonephritis                              |                                  |
| Hypertensive nephrosclerosis                    |                                  |
| Polycystic kidney disease                      |                                  |
| Other                                           |                                  |
| Medication use                                  | n (%)                            |
| ACE inhibitors                                  |                                  |
| Angiotensin II receptor blockers (ARBs)         |                                  |
| ACE inhibitors or ARBs                         |                                  |
| Diuretics                                       |                                  |
| Calcium channel blockers                        |                                  |
| Beta blockers                                   |                                  |
| Aspirin                                         |                                  |
| Antiplatelet drugs (not including aspirin)     |                                  |
| Anti-inflammatory (regularly scheduled use)     |                                  |
| Oral glucocorticoids                            |                                  |
| Cholesterol lowering medications (niacin, fibrates, statins) |                 |
| Opioid analgesic                                |                                  |
| Non-warfarin anticoagulant |
|---------------------------|
| ^a CKD-EPI eGFR equation.\textsuperscript{34} |
| ^b Smoker within the last 10 years, but not currently smoking. |
Micro-Particle Curcumin for the Treatment of Chronic Kidney Disease-1 (MPAC-CKD-1)

Statistical Analysis Plan (SAP)

Supplemental Document
Supplemental Table 1. Changes to the published MPAC-CKD-1 protocol (Weir MA et al. *Can J Kidney Health Dis.* 2018;5:1-9)

| Published protocol | Change in SAP | Reason for change |
|--------------------|---------------|-------------------|
| “Using these data, enrolling 250 patients per group will allow an 87% power (α=0.025) to exclude a difference of 21 mg/mmol. To allow for loss to follow-up, we expect to recruit up to an additional 75 patients to reach a minimum of 250 patients per arm with complete follow-up data.” | “Enrolling a total of 518 patients and accounting for 5% loss to follow-up allows for 82% power (α = 0.025) to detect a geometric mean ratio of 0.75, assuming a standard deviation of the 6-month log-transformed albumin-to-creatinine ratio of 1.0” | We will follow the recently published methods used by Heerspink et al. (Lancet Diabetes Endocrinol. 2019;7:128-39) for between-group comparisons involving albumin-to-creatine data. These methods were published after the creation of our original protocol. We have updated our sample size calculations to reflect this. |
| “For changes in eGFR, we will have 90% power (α = 0.025) to exclude a difference of 2.3 mL/min/1.73m$^2$ between treatment and control groups (using a standard deviation of 4 mL/min/1.73m$^2$).” | “For the between-group difference in change in eGFR (6-month eGFR minus pre-randomization eGFR), we will have 81% power (α = 0.025) to exclude a difference of 1.65 mL/min per 1.73 m$^2$ between treatment and control groups (using a standard deviation of the change of 5.8 mL/min per 1.73 m$^2$).” | We have updated our sample size calculations using the overall standard deviation of the change in eGFR in the MPAC-CKD-1 study (without any by-group computations); we have also updated the detectable between-group difference to more closely align with observed effects in Inker et al. (J Am Soc Nephrol. 2019;30:1735-1745). |
| “We will use two-sample t-tests to compare changes in the co-primary outcomes.” | “The geometric mean ratio of 6-month urinary albumin-to-creatinine ratio will be estimated using linear regression, where the outcome is the log-transformed average of two 6-month follow-up visit urinary albumin-to-creatinine ratio measurements minus log-transformed average of two pre-treatment urinary albumin-to-creatinine ratio measurements, adjusting for a treatment indicator variable and the log-transformed average of two baseline urinary albumin-to-creatinine ratio measurements.” | We will follow the recently published methods used by Heerspink et al. (Lancet Diabetes Endocrinol. 2019;7:128-39) for between-group comparisons involving albumin-to-creatine data. We have also updated the planned method of analysis for the outcome of change in eGFR; linear regression will be used instead of a t-test. We expect that the estimates and P values will be virtually identical in both methods (linear regression vs. t-test). |
| “We will use a two-sample t test to compare changes in hemoglobin A1c between the 6-month and baseline values. The risk of the composite outcome of loss of ≥30% of baseline eGFR, ESRD, or death will be compared between groups using logistic regression analysis. The proportions of patients discontinuing study capsules and experiencing adverse events will be compared between groups using the chi-square test.” | Estimates of between-group differences in the secondary outcomes will be presented with 95% confidence intervals, without formal hypothesis testing and reporting of P values, in order to reserve the overall type I error rate of 0.05 for the two primary outcomes. Hypothesis tests for between-group differences in safety-related outcomes will be tested at the 0.05 significance level. The safety-related outcomes are: (i) minor side-effects including minor nausea, headache, diarrhea, yellow stool, temporary giddiness, localized swelling of the skin, or hives; (ii) bleeding; (iii) hypoglycemia. | These changes are in accordance with new guidelines regarding multiple testing and adjustment for multiplicity in Harrington et al. (N Engl J Med. 2019;381:285-286). Hypothesis tests for outcomes related to safety will be performed according to New England Journal of Medicine publication guidelines. (https://www.nejm.org/author-center/new-manuscripts) |


“We will record baseline characteristics pertinent to the progression of CKD and adjust the final point estimates of risk for these variables using linear regression analysis. Characteristics that will be included in the multivariable regression model are the following: age, sex, tobacco use, blood pressure, glycemic control, use of angiotensin-convertingenzyme inhibitors or angiotensin receptor blockers, use of aldosterone antagonists.”

“In sensitivity analyses, we will repeat the two primary analyses while (i) accounting for randomization strata (centre and pre-randomization diabetes); (ii) accounting for randomization strata and adjusting for variables associated with disease progression including age, sex, tobacco use, blood pressure, baseline use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and baseline use of aldosterone antagonists.”

We have updated the planned sensitivity analyses to account for randomization strata, with and without adjustment for baseline characteristics. We do not anticipate that accounting for randomization strata and/or adjustment for pre-randomization variables will change results in any meaningful way.

“To confirm the improved bioavailability reported with micro-particle curcumin, and to strengthen any relationship between micro-particle curcumin and any outcomes we identify, we will measure serum trough levels of curcumin and its major metabolites in the first 25 participants randomized.”

“To confirm our micro-particle curcumin was bioavailable, and to strengthen any relationship between micro-particle curcumin and any outcomes we identify, serum levels of curcumin and its major metabolites were measured in the first 30 participants 3 months after randomization (including patients taking micro-particle curcumin and those taking placebo).”

Serum curcumin and its major metabolites were collected in the first 30 patients randomized; the measurements were not necessarily taken prior to treatment (the values are not necessarily trough levels).

The published protocol contained general information on inclusion and exclusion criteria.

The SAP includes detailed information on inclusion/exclusion criteria.