Trials

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Evaluating a multicomponent intervention for managing kidney outcomes among patients with moderate or advanced chronic kidney disease (CKD): protocol for the Strategies for Kidney Outcomes Prevention and Evaluation (SKOPE) randomized controlled trial

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Abstract

Background Chronic kidney disease (CKD) poses a global health challenge with high morbidity and mortality rates. Early detection and prompt intervention are critical in preventing progression to end-stage kidney disease (ESKD) and cardiovascular complications. Effective CKD management requires comprehensive care packages that integrate both pharmacological and non-pharmacological interventions within collaborative, team-based models, aiming to enhance patient outcomes and overall quality of life. The goal of the Strategies for Kidney Outcomes Prevention and Evaluation (SKOPE) study is to establish effective multicomponent intervention (MCI) strategies for evaluating and preventing kidney outcomes in patients with moderate to advanced CKD within primary care settings in Singapore.

Methods This study is a 3-year randomized controlled trial among 896 participants aged between 40 and 80 years with moderate or advanced CKD in five government-subsidized polyclinics in Singapore. The components of the MCI are (1) nurses/service coordinators trained as health coaches for motivational conversation and CKD-specific lifestyle counseling on diet and exercise, using a hybrid follow-up approach of in-person, telephone, and secure video meetings; (2) training physicians in algorithm-based standardized management of CKD; (3) subsidy on SGLT2i medications for CKD; and (4) regular CKD case review meetings. The primary outcome is the estimated glomerular filtration rate (eGFR) total slope from randomization to final follow-up at 36 months.

Discussion If shown to be effective, cost-effective, and acceptable, SKOPE should be considered for scaling country-wide and in similar regional healthcare systems.

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Keywords Chronic kidney disease, Estimated glomerular filtration rate, Quality of life, Cardiovascular, Multicomponent intervention, Motivational counseling, Telephone follow-up

Introduction

Background and rationale {6a}

Chronic kidney disease (CKD) is a major public health threat associated with high morbidity and mortality [1]. It is estimated that by 2040, CKD will become the fifth leading cause of death globally, reflecting one of the steepest increases of any major cause of death, including in Singapore [2, 3]. The number of people with CKD requiring dialysis is projected to reach over 9 million globally by 2030 [4]. Singapore ranks as one of the top five countries with the highest CKD incidence rates in the world [5]. Diabetes and hypertension are the main causes of CKD, regardless of socioeconomic status [1]. Environmental pollution, pesticides, infections, water, analgesic abuse, and herbal medications are additional etiologies [6]. Early detection of CKD and timely institution of treatment by primary care clinicians is important to prevent progress adverse clinical outcomes, including end-stage kidney disease (ESKD), cardiovascular disease, and increased mortality.

A range of evidence-based therapies can prevent or delay CKD progression and the onset of cardiovascular diseases. These include lifestyle strategies of regular physical activity [7, 8], weight management [9], moderate dietary salt [10, 11], protein restriction [12, 13], pharmacological strategies for blood pressure (BP) and glucose control, such as treatment using renin-angiotensin system blockade [14–16], statins [17], and sodium-glucose cotransporter-2 inhibitors (SGLT2i) [18]. SGLT2is are recommended by major treatment guidelines in people with CKD due to diabetes. The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) findings extend their indications for patients without diabetes and CKD especially those with albuminuria [19].

Although treatments (as described above) have proven efficacy for preserving kidney function in patients with established CKD, large gaps remain in their translation into routine clinical practice, resulting in poor outcomes. It is widely agreed that patients with CKD need a multifaceted approach for optimal ESKD and cardiovascular disease (CVD) prevention and improved quality of life, as it is more effective than targeting a single drug or risk factor. For instance, a study of 160 diabetic patients with microalbuminuria showed that addressing multiple risk factors reduced cardiovascular and microvascular events by about 50%, significantly more than single-factor interventions [20]. However, multiple barriers at the patient, physician, and health systems (including cost) levels hinder the care of CKD [21]. Specific CKD care "packages" consisting of pharmacologic and non-pharmacological interventions coupled with innovative ways of care delivery are needed in the real world [22].

Systematic reviews of randomized controlled trials (RCTs) have shown that multicomponent implementation strategies are more effective than single strategies in overcoming barriers to hypertension control [23]. Team-based care, where nurses, pharmacists, and allied health workers share disease management responsibilities with primary care physicians, has been particularly effective for BP control [23]. Patient-centered health coaching has been an integral component of these strategies [23]. Similar team-based collaborative care models have succeeded in managing chronic conditions such as diabetes, depression, and coronary artery disease [24].

Our experience with COBRA-BPS strategies in South Asia and SingHypertension trial strategies in Singapore indicate the effectiveness of multicomponent approaches with team-based collaborative care models [25, 26]. These models include health coaching by community health workers or nurses and structured care pathways. However, empirical evidence on strategies to improve the effectiveness of CKD care remains limited. Moreover, previous pragmatic trials in patients with CKD lacked focus on kidney function outcomes, i.e., estimated glomerular filtration rate (eGFR) or ESKD, or were non-randomized evaluations, thereby limiting their broader applicability [27, 28]. Thus, there is an urgency for an innovative, effective, and potentially scalable "real world" CKD care program to preserve kidney function and improve cardiovascular health in patients with moderate-advanced CKD in primary care settings. This multicenter RCT aims to develop effective strategies for kidney outcomes evaluation and prevention (SKOPE) among patients with moderate or advanced CKD in primary care settings in Singapore. The goal is to empower patients with knowledge to reduce unhealthy behaviors and ensure that all their health needs are comprehensively addressed via the SKOPE intervention strategies, thereby improving their kidney function and quality of life. In this paper, we describe the protocol related to the primary objectives of the SKOPE study.

Objectives {7}

The SKOPE components include:

1. Nurses/service coordinators trained as health coaches for motivational conversation and CKD-specific lifestyle counseling on diet and exercise, using a hybrid follow-up approach of in-person, telephone, and secure video meetings
2. Training physicians in algorithm-based standardized management of CKD
3. Subsidy on SGLT2i medications for CKD
4. Regular CKD case review meetings

Primary objectives

The primary objectives are (1) to determine whether SKOPE intervention integrated into the primary care system will be more effective than usual care on the primary outcome of preserving kidney function (eGFR slope), and the secondary outcomes of lowering cardiovascular risk, and improving health-related quality of life (HRQoL) in patients with CKD; (2) to determine the incremental cost-effectiveness of SKOPE compared with usual care on quality-adjusted life-years (QALYs) gained from the health system perspective. We will also perform a budget impact analysis from this same perspective.

Secondary objectives

The secondary objectives of this study are (1a) to assess the facilitators, barriers, and acceptability of SKOPE from the perspectives of key stakeholders (patients, nurses, physicians, pharmacists, dietitians, clinic managers), and (1b) to explore the impact of a potential or existing pandemic (e.g., COVID-19) on CKD care delivery. (2) To perform a mediation analysis and estimate the extent to which changes in lifestyle behaviors (body mass index, diet, physical activity), clinical risk factors (BP, blood glucose, lipids), and pharmacologic therapy (number and types of antihypertensive and glucose-lowering medications, and statins) mediate the effect of SKOPE versus usual care on preserving kidney function.

Hypotheses

The hypotheses are that, in adults with CKD receiving treatment at primary care clinics in Singapore,

1) An innovative, structured "SKOPE" CKD care program is more effective than usual care in preserving kidney function.
2) SKOPE is cost-effective relative to usual care in terms of cost per QALYs gained from the health system perspective based on established benchmarks for cost-effectiveness.

Trial design {8}

This study uses a RCT design involving two parallel groups equally allocated to the intervention and usual care conditions ($n=448$ per arm; 1:1 allocation). Randomization will be done at the participant level stratified by the polyclinics. In this study, the research team aims to determine whether the SKOPE intervention demonstrates superiority relative to the usual care group. CKD patients of age ≥ 40 years and < 80 years will be recruited from five socioeconomically diverse primary care clinics (polyclinics) and followed up for 3 years.

Methods: participants, interventions, and outcomes

Study setting {9}

All research activities will be conducted in three SingHealth Polyclinics (SHP) (Bukit Merah, Bedok, and Eunos Polyclinics) and two National University Polyclinics (NUP) (Queenstown and Clementi Polyclinics) in Singapore, including data collection and delivery of the intervention.

Eligibility criteria {10}

Participants must satisfy all of the inclusion criteria and none of the exclusion criteria to be enrolled in the study.

Inclusion criteria

1. Patients with a persistent reduction in eGFR (Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [29]) ≥ 15 and < 60 ml/min/1.73 m^2 (or if diabetes, ≥ 15 and < 70 ml/min/1.73 m^2) for at least 3 months, based on two eGFR readings at least 3 months apart, with the most recent eGFR being measured within 12 months of baseline evaluation
2. Receiving care at the participating polyclinic, except for Eunos Polyclinic, for at least 1 year at the time of recruitment, or receiving care at any SingHealth Polyclinic for the past year for Eunos Polyclinic
3. Age ≥ 40 and < 80 years
4. Singaporean or permanent resident

Exclusion criteria

1. On kidney replacement therapy
2. Pregnancy or breastfeeding
3. Known terminal illness
4. Recent hospitalization during the last 3 months
5. History of leg or foot ulcers, severe mental illness, prior kidney transplant

6. Inability to provide informed consent

Who will take informed consent? {26a}

The trained clinical research coordinators (CRCs) will obtain consent from the participants under the supervision of the clinic physician. The informed consent form must be signed by the participants or their legally authorized representatives before participation in the study. Documentation of the date informed consent will be obtained and a notation that a signed copy is given to the participant should be recorded in the subject's records. Signed consent forms must remain in each participant's study file and be available for verification by study monitors at any time.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

There are no additional consent requirements for collecting and using participant data and biological samples. Biological samples will not be analyzed. Consent for data collection is given by agreeing to participate in the study.

Interventions

Explanation for the choice of comparators {6b}

The study aims to evaluate if the proposed SKOPE intervention strategies are better than existing usual care for patients with CKD. The usual care will serve as the comparator for evaluating the effectiveness and cost-efficiency of the SKOPE interventions while ensuring patient safety and ethical standards, thereby providing insight as to whether the SKOPE interventions can be adopted into clinical practice for patients with CKD.

Intervention description {11a}

The intervention is a structured multicomponent intervention (MCI) comprising:

1. Training nurses or service coordinators as health coaches and hybrid follow-up approach of in-person, telephone, and secure video sessions

At least two nurses or service coordinators (preferably bilingual- Chinese, Malay, Tamil in addition to English speaking) at each of the 5 polyclinics will be trained over the Zoom platform in motivational conversation (MC), and nutritional assessment, lifestyle counseling and self-care for prevention of CKD and CVD. Training on MC will be provided over 4 h/half day by a psychologist, and nutritional assessment and lifestyle counseling will be given by a registered dietician in 4 sessions over 2 weeks, followed by a post-test. Refresher training sessions will also be conducted annually until the trial's end. Additionally, a refresher training of 1 session will be conducted at 3 months from baseline. The MC curriculum developed for the SingHypertension trial will be adapted for CKD. The counseling approach is intended to help the patients resolve problems and make decisions to facilitate the patient's participation and empowerment in care, and to consider the patients' priorities along with the patient and set goals for self-care. A contextually relevant "nutrition and physical activity curriculum" will be developed in consultation with the Health Promotion Board (HPB). The recommendations will be based on Kidney Disease Improving Global Outcomes (KDIGO) management guidelines for CKD-specific diet and exercise. This will include limiting dietary sodium, low to moderate protein restriction according to CKD stage, preferably with at least 50% from plant-based sources, and increased low glycemic impact fruit [30], vegetable intake, and physical activity (at least 150 min per week of moderate-intensity), accounting for the presence of diabetes and other co-morbidities [31]. Moreover, smoking cessation, adherence to antihypertensive and anti-diabetic medications and statins, and avoidance of non-steroidal anti-inflammatory drugs (NSAIDs) and nephrotoxic agents will be emphasized. Home BP monitoring will be encouraged. The health coach's first session will be 35 to 40 min in duration, and follow-ups in 1 month, 3 months, and then every 3 months for the project's duration (3 months to 3 years).

All consultations will be delivered via a hybrid approach of in-person or telehealth/video meetings with a follow-up checklist (Additional file 1). Dedicated trial phones at the clinic will be used for video meetings with disabled texting and no recording features to protect patient confidentially.

2. Training physicians in algorithm-based standardized management of CKD and hybrid care delivery

A standardized treatment protocol based on KDIGO guidelines for CKD management, which includes risk stratification for ESKD using Southeast Asia Kidney Failure Risk Equation (SEA KFRE) risk equation (recalibrated by our team for Singapore [32], and for CVD will be reviewed and finalized by a team of nephrologists, cardiologists, dietician, sports physicians and pharmacologists in consultation with SingHealth primary care physicians. Based on the standardized treatment protocol developed, a physician management checklist (Additional file 2) will be designed. Primary care physicians (at least two from each of the 5 clinics) will be invited for training, and intensively trained over the Zoom platform in CKD management strategies as per trial protocol. The physicians will be trained in standardized CKD management,

including nonpharmacologic and pharmacologic treatment algorithms, using a case-based curriculum over 2 sessions (Fig. 1). Refresher training sessions (1 session) also will be conducted yearly till the trial ends.

The target BP will be < 130/80 mm Hg, which takes into account the recommendations of KDIGO and the National Institute for Health and Care Excellence (NICE). A lower systolic blood pressure (SBP) target < 120 mmHg would be pursued in certain patients (i.e., with albumin-to-creatinine ratio (ACR) 30 mg/mmol or higher), if acceptable to the treating physician and the patient. Single pill combination (SPC) including renin–angiotensin–aldosterone system (RAAS) blocker and Hydrochlorothiazide-like diuretic (e.g., Hyzaar) will be offered to patients with eGFR ≥ 30 ml/min/1.73 m^2. For those with eGFR < 30 ml/min/1.73 m^2, individual drug prescriptions will be preferred. RAAS blockers will be the first-line antihypertensive agents, especially in the presence of diabetes and albuminuria 3 mg/mmol or higher, followed by thiazide-like diuretic and then calcium channel blocker

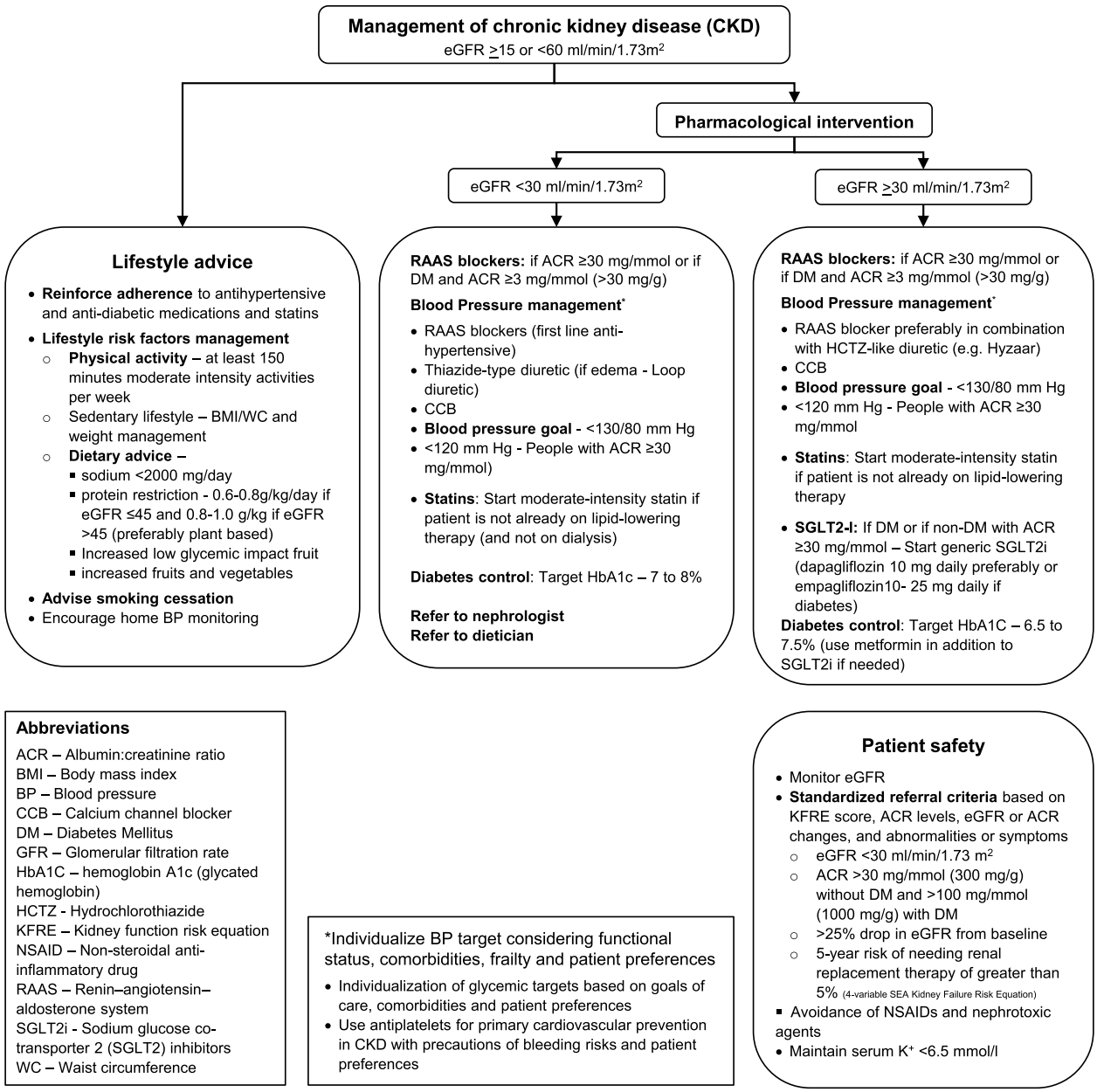

Fig. 1 CKD management algorithm for SKOPE patients

(CCB). A loop diuretic (torsemide or furosemide) would be preferred over thiazide in the presence of edema. Moderate-intensity statin will be started on patients not already on lipid-lowering therapy.

All patients with eGFR ≥ 30 ml/min/1.73 m^2 and (1) diabetes (regardless of ACR level) or (2) non-diabetes and ACR 30 mg/mmol or higher will be recommended for generic SGLT2i (dapagliflozin 10 mg daily preferably or empagliflozin 10–25 mg daily if diabetes). Other antidiabetic agents will be adjusted if needed.

Target glycated hemoglobin will be between 6.5 and 7.5% (or between 7 and 8% if eGFR is less than 30 ml/min/1.73 m^2) based on the KDIGO guidelines. Serum potassium and creatinine will be checked in 4 to 8 weeks on patients initiated on RAAS blockers or SGLT2i and flagged for action if levels > 20% of baseline.

Initial physician consultation would last about 15 min and would be completed preferably within 3 months post-randomization. Physician follow-up would be scheduled every 6–8 weeks and then every 3–4 months. At least one visit per year with a SKOPE-trained physician should be done. However, the frequency of follow-up clinic/remote visits will be determined and adjusted by level of risk factor (BP, glucose), albuminuria and eGFR changes, and symptoms, feedback from the nurse kidney health coach, at the discretion of the treating physician. Standardized referral criteria (Fig. 2) based on KFRE score, ACR levels, eGFR or ACR changes, and abnormalities or symptoms will be implemented. In every consultation and follow-up of intervention patients, the physician will also complete the physician management checklist (Additional file 2) with a total contact time of approximately 15–20 min.

3. Regular CKD case review meetings

Regular CKD case review meetings will be held monthly for the first 2 months and then once every 3 months among trained nurses/service coordinators (health coaches), dieticians, and trained physicians to review the progress and CKD care plan with subsequent communication with the intervention patients, as needed. For each patient reviewed in the meeting, the health coaches will record the reasons for review, key points discussed, and action items for further patient management.

4. Subsidy of SGLT2i for CKD

At the end of each year after randomization, patients in the intervention arm who take SGLT2i (e.g., dapagliflozin or empagliflozin) as prescribed will receive a $30 voucher, regardless of whether they were already using SGLT2i before the trial or started during the trial. However, if the participants withdraw from participation during the study, they will not receive any voucher for SGLT2i treatment after the withdrawal.

Usual care

Physicians and nurses who are not trained in SKOPE treatment algorithms will treat patients in the usual care arm. There will be no restrictions on prescriptions for RAAS blockers, SGLT2i, or lifestyle advice. However, patients in usual care should not receive care from a SKOPE-trained health coach or physician trained in SKOPE intervention except in case of emergency, and

- eGFR <30 ml/min/1.73m^2
- >25% drop in eGFR from baseline
- 5-year risk of needing renal replacement therapy of greater than 5% - measured using the 4-variable SEA Kidney Failure Risk Equation.
- Non-diabetics with severely increased albuminuria (24 hr urine albumin >300 mg, uACR >30 mg/mmol (300 mg/g))
- Diabetics with >100 mg/mmol albuminuria (uACR >100 mg/mmol (1000 mg/g))
- Very high-grade albuminuria (>300 mg/mmol (3000 mg/g)) will require emergent nephrology referral, especially if non-diabetic.
- Gross hematuria or red cell cast in urine
- Complications of CKD (e.g., anemia, acidosis, hyperkalemia, hyperphosphatemia, hyperparathyroidism)
- Autosomal polycystic kidney disease (PKD)
- Patient's level of disease exceeds the level of comfort of the primary care provider

Fig. 2 Nephrologist referral criteria

will not receive trial-related subsidy on SGLT2i. However, advice regarding the management of CKD as per usual practice will continue.

Criteria for discontinuing or modifying allocated interventions {11b}

Participants may choose to withdraw from the study at any time. However, any of the participants' data collected until the time of withdrawal will be kept and analyzed. Participants may be withdrawn if they become ineligible, such as if the person has ESKD or cancer during the study. Involuntary withdrawal may occur due to failure to follow instructions, health or safety concerns, need for treatment not permitted in the study, or study cancelation. If this happens, the participant will be notified by phone or email. Study data collected up to that point will be retained unless otherwise requested.

Strategies to improve adherence to interventions {11c}

As mentioned in the "intervention description," both physicians and health coaches (site interventionists) will be trained before the intervention and retrained yearly. The health coaches will complete the follow-up checklist (Additional file 1) for each telephone follow-up, and trained physicians will complete the physician management checklist for each consultation. Case review meetings and subsidies for SGLT2i treatment will be tracked by a checklist and a log, respectively. All checklists and logs will be reviewed regularly. Additionally, the Principal Investigator (PI) and site interventionists will meet regularly to discuss challenges, share solutions, and ensure everyone is aligned. Standardized materials, including intervention slides, talking points, and a facilitator guide, will reinforce adherence.

Multiple strategies will be adopted to support participants' adherence to the intervention. During the informed consent process, the CRC will ensure that participants fully understand the trial requirements and provide informed consent voluntarily. Throughout the trial process, the needs and preferences of participants will be prioritized. Moreover, 6 monthly telephone follow-ups will be done to monitor healthy behavior, medication adherence, and adverse events, and reimbursement will be provided to the participants for completing each yearly physical visit.

Relevant concomitant care permitted or prohibited during the trial {11d}

Relevant concomitant care is permitted during the trial.

Provisions for post-trial care {30}

The intervention is delivered by leveraging the existing healthcare system, which will also deliver post-trial care. The likelihood of harm from participation in the trial is low.

Outcomes {12}

Effectiveness outcomes

The outcome assessors will collect the outcome data yearly for all patients. The outcomes collected via participant interview include medication adherence, physical activity (international physical activity questionnaire (IPAQ) [33]), diet (8 questions adapted from locally validated 163-item semi-quantitative food frequency questionnaire (FFQ) [34]), and quality of life (EQ-5D-5L [35]). Data on medications, anthropometric measurements, BP, CVD risk score (if available), and laboratory tests will be extracted from electronic medical records (EMR), for the most recent visit before the assessment date. The clinical data will be linked with the Singapore Registry of Renal Disease for information on vital statistics and ESKD. Deaths from myocardial infarction, heart failure, or stroke (per ICD-10 codes) will be categorized as CVD deaths. The outcome assessors will also call the patients over the telephone at 6-month intervals on adverse events. Additionally, they will also extract process outcomes measures from the general practitioner (GP) and nurses' notes.

Primary outcome measures

The primary outcome will be the eGFR total slope from randomization to final follow-up at 36 months [36]. eGFR will be calculated using the CKD-EPI formula [29]. For the 3-year trial, 0.75 mL/min/1.73 m^2/year eGFR slope reduction corresponds to 27% (95% CI, 20–34%) lower average risk for ESKD and is considered an acceptable endpoint for clinical trials by the US FDA and European Regulatory Agency [36].

Secondary outcome measures

1. Mean change in CVD risk score at 12, 24, and 36 months from the baseline as measured by The Million Hearts Longitudinal Atherosclerotic Cardiovascular Disease (ASCVD) Risk Assessment score [37]. The score is based on age, sex, race, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, treatment with statin, systolic BP, BP lowering medication use, diabetes status, current smoker and aspirin therapy.
2. Mean change in quality of life at 12, 24, and 36 months from the baseline will be assessed using EQ-5D-5L [35].

3. Proportion of receiving guideline-recommended therapies: SGLT2i, RAAS blockers, and statins at 12, 24, and 36 months from the baseline

Ancillary outcome measures

Other secondary outcomes of interest at 36 months will be as follows:

1. Proportion of subjects who experience either one of the following composite outcome and individual outcome of
    a. Incident eGFR < 30 ml/min/1.73 m^2;
    b. Incident eGFR < 45 ml/min/1.73 m^2;
    c. Incident eGFR < 15 ml/min/1.73 m^2;
    d. Incident ACR > 30 mg/mmol (> 300 mg/g);
    e. Incident dialysis; or
    f. Major adverse cardiovascular events (MACE: composite of total death, myocardial infarction, coronary revascularization, stroke, and hospitalization because of heart failure) [9].
2. Proportion of subjects who experienced major adverse kidney events (MAKE)
    a. Proportion of subjects with at least 40% decline in baseline eGFR or kidney replacement therapy (KRT) with mortality
    b. Proportion of subjects with at least 40% decline in baseline eGFR or KRT without mortality
    c. Proportion of subjects with at least 50% decline in baseline eGFR or KRT with mortality
    d. Proportion of subjects with at least 50% decline in baseline eGFR or KRT without mortality
3. Mean change from baseline in KFRE score [38]
4. Proportion of subjects who experienced albuminuria defined as ACR ≥ 3 mg/mmol (30 mg/g)
5. Individual outcomes of the proportion of subjects who experienced
    a. All-cause mortality
    b. CVD deaths
    c. Hospital admission due to coronary heart disease (CHD), heart failure, or stroke
6. Lifestyle
    a. Mean change from baseline in a healthy diet
    b. Median change from baseline in physical activity
    c. Mean change from baseline in BMI
7. Adherence to medications
    a. Mean change from baseline in adherence to antihypertensive medications
    b. Mean change from baseline in adherence to antidiabetic medications
8. Mean change from baseline in antihypertensive medication (all and class specific) therapeutic intensity score (summary measure that accounts for the number of medications and the relative doses a patient received) [39]
9. Mean change from baseline in Framingham risk score (FRS) [40]

Cost-effectiveness outcomes

Within the trial cost per QALY gained will be based on incremental costs using an Activity Based Costing Approach, cost-offsets based on differential healthcare utilization based on medical and billing data, and self-reported changes in health-related quality of life based on responses to the EQ-5D-5L [35] at key assessments. Lifetime cost-effectiveness will be based on a disease progression model that converts changes in CVD risk scores to changes in lifetime QALYs. All analyses will be from the health system perspective as recommended by Singapore's Agency for Care Effectiveness (ACE).

Participant timeline {13}

The participant timeline is shown in Table 1.

Sample size {14}

The sample size calculated for the primary effectiveness aims to compare the total slope of change in eGFR at month 36 from the baseline between the intervention and usual care group. We anticipate a conservative effect size of at least 0.21 for the intervention on eGFR slopes with a less steep decline in the slope in the intervention group than the usual care group. The assumptions are based on the SingHypertension subgroup analysis of CKD patients and trials of SGLT2i [41]. Since SKOPE promotes CKD-specific lifestyle and pharmacologic therapies delivered via team-based structured care, its actual effect size is expected to be greater than 0.21 [42]. With an estimated standard deviation of 3.6 ml/min/1.73 m^2 per year for the total slope of decline in eGFR, and a difference of 0.75 ml/min/1.73 m^2 per year in the total slope corresponds to an effect size of 0.21 [13, 42]. The required total sample size will be 894 subjects (447 per arm) for 80% power at a two-sided 5% significant level, allowing for 20% drop-outs [41]. We plan to recruit an equal number of participants from SHP and NUP, with

Table 1 Timeline of study events for participants

Schedule	Baseline	Post-allocation[1]						
		1m after starting RAAS blocker, SGLT2i, or statin	6m	12 m	18 m	24 m	30 m	36 m
ENROLLMENTS								
Eligibility assessment	✓							
Informed consent	✓							
INTERVENTIONS								
Intervention group		♦—	—	—	—	—	—	—♦
Usual care group		♦—	—	—	—	—	—	—♦
ASSESSMENTS								
Socio-demographic information	✓							
Personal medical history	✓							
Family medical history	✓							
CKD awareness	✓			✓		✓		✓
Dietary questionnaire	✓			✓		✓		✓
Physical activity	✓			✓		✓		✓
Tobacco smoking	✓			✓		✓		✓
Self-reported frequency of home blood pressure monitoring	✓			✓		✓		✓
Self-reported frequency of home glucose monitoring	✓			✓		✓		✓
EQ-5D-5L	✓			✓		✓		✓
10-year CVD risk score	✓			✓		✓		✓
Office-based blood pressure (in clinic)	✓			✓		✓		✓
Anthropometric measures : weight and	✓			✓		✓		✓
Anthropometric measure: height	✓							
Polyclinic visit or hospitalization since last follow up				✓		✓		✓
Panel lab tests - Serum sodium, potassium, creatinine, ACR, fasting blood glucose, total cholesterol. high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, glycated hemoglobin (if patient has diabetes) - eGFR - Optional tests[2]: serum albumin, calcium, phosphorous, blood urea nitrogen, serum PTH, urine strip test (blood, protein)	✓			✓		✓		✓
Serum creatinine (for study only, 3ml blood draw)			✓					
Safety monitoring laboratory tests[3] - Renal (serum sodium, potassium, chloride, creatinine) - Optional test[2]: serum creatinine kinase		✓						
Adverse event reports			✓	✓	✓	✓	✓	✓

447 participants in each cluster. Since the two NUP Polyclinics will recruit an equal number of participants, this results in (223.5) 224 participants from each, for a total of 448 from NUP. An additional 448 participants will be recruited from SHP, bringing the overall total to 896 participants.

For the secondary objectives (1a and 1b), 40 patients and healthcare professionals will be enrolled for pre-, during, and post-intervention.

Recruitment {15}

The trial will be conducted in 5 polyclinics in Singapore in two regional health clusters. The primary care team can identify and direct potential patients upon review of EMR to the trained CRCs at the clinic.

Upon permission from the primary physician/care team, the study team will also pre-screen the list generated via the Electronic Health Intelligence System (eHIntS) by the admin or data team and shortlist potential participants. CRC will collaborate with the physician to verify the eligibility of shortlisted patients. Those potentially eligible will be contacted on the phone by the CRC with approval from the physician/care team to invite them to participate in the trial and arrange a convenient time for a screening visit for interested patients. An invitation letter will be sent to the patients before they are called, and CRCs will call them following the standard phone script. The CRC will also approach potentially eligible patients, who visit the clinic in person. The CRC will complete the eligibility assessment and written informed consent will be obtained in person or via telephone. Screening for conditions like mental illness and terminal illness need access to patient's medical records, where the CRC may face challenges. In that case, the CRC can do the preliminary assessment first, and formal verification of mental competence will be done when the patient visits the intervention and/or usual care physician in the clinic later.

The recruitment approaches in this study will be dynamic. Ongoing monitoring of recruitment progress will guide decisions on adapting these approaches as needed.

Assignment of interventions: allocation

Sequence generation {16a}

After the baseline assessment, patients will be randomized to receive SKOPE (intervention group) or usual care (control group) in an open-label fashion according to a 1:1 allocation ratio. Randomization will be stratified by polyclinic and will be generated using the permuted blocks web-based randomization technique by a statistician. Block sizes will be masked to clinical investigators, other trial team members involved in patient recruitment, and the trial patients.

Concealment mechanism {16b}

A central web-based randomization system provided by the Singapore Clinical Research Institute (SCRI) will be used to randomize patients. The system will randomize patients according to the randomization list upon entering the patient's initials, date of birth, and trial eligibility status. Access to the system will be secured through an access-controlled login.

Implementation {16c}

Upon randomization, the system will notify the site investigator by an automated email. Meanwhile, a uniquely identified patient study ID number will also be generated by the randomization system for the randomized patient. Randomization can also be done before baseline assessment for eligible and consenting patients.

Assignment of interventions: blinding

Who will be blinded {17a}

Blinding of participants and healthcare providers is not possible due to the nature of the intervention. However, the outcome assessors will remain blinded.

Procedure for unblinding if needed {17b}

Not applicable. Due to the study design, participants and healthcare providers are not blinded.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Baseline/screening assessment

Baseline assessments will be completed for patients who are eligible and provided consent. CRC will administer the baseline questionnaire (either in-person or virtually, depending on the patient's preference. Information on socio-demographics, family medical history, CKD awareness (based on the following two questions: "have you ever been told that": (1) "you have kidney problems, weak kidneys, or kidney disease?"; (2) "your kidney problem was caused by diabetes?), diet (8 questions adapted from locally validated 163-item semi-quantitative FFQ [34]), physical activity (IPAQ [33]), tobacco use (questions from WHO questionnaire), CKD self-care (self-reported frequency on home BP and glucose monitoring), quality of life (EQ-5D-5L [35]) will be collected. The details of medications prescribed, co-morbidities, BP, BMI, CVD risk score (if available), and the labs will be obtained from the medical records for the most recent visit before the assessment date. An option of in-person assessment in the clinic will be provided for those who prefer to

complete the assessment in person in clinic or to overcome any unexpected technical challenges for a virtual interview. For such patients, the baseline questionnaire will be administered in person. Data on co-morbidities, medications, anthropometric measurements, BP, CVD risk score, and laboratory tests, will be extracted from EMR. All laboratory measurements will be done using protocols that adhere to international standards. Serum creatinine measurements will be traceable to isotope dilution mass spectrometry (IDMS) reference standard and reported as CKD-EPI eGFR, which has been validated in patients with CKD in Singapore [29, 43].

Follow-up and outcomes assessment

During the 3-year follow-up, independent outcome assessors will follow up with the patients and perform outcomes assessments using a hybrid follow-up approach (either virtual or in-person) based on the patient's preference. The outcome assessors will collect the outcome data yearly for all patient, using the same tools as baseline, and information on tobacco use (based on WHO questionnaire), physical activity (IPAQ [33]), diet (8 questions adapted from locally validated 163-item semi-quantitative FFQ [34]), healthcare use since last assessment, CKD awareness(based on the following two questions: "have you ever been told that": (1) "you have kidney problems, weak kidneys, or kidney disease?"; (2) "your kidney problem was caused by diabetes?), CKD self-care (self-reported frequency on home BP and glucose monitoring), and quality of life (EQ-5D-5L [35]). The details of medications prescribed, BP, BMI, and the labs will be obtained from the medical records, for the most recent visit before the assessment date. The outcome assessment questionnaire will be administered in person for patients who prefer to complete the outcome assessment in person in the clinic or in situations needing to overcome any unexpected technical challenges for a virtual interview. Data on medications, anthropometric measurements, BP, CVD risk score (if available), and laboratory tests, will be extracted from EMR. The clinical data will be linked with the Singapore Registry of Renal Disease for information on vital statistics and ESKD. Deaths from myocardial infarction, heart failure, or stroke (per ICD-10 codes) will be categorized as CVD deaths.

In addition, the outcome assessors will also call the patients over the telephone at 6-month intervals on adverse events. At 6 months from baseline, a serum creatinine test will be performed in the polyclinic for patients from both groups. The outcomes assessors will also extract process outcomes measures from the GP and nurses' notes.

Cost data collection

Intervention costs will be tracked using administrative records and standard cost collection instruments that capture all relevant labor, materials, and participant costs using an Activity Based Costing (ABC) approach that has been applied in numerous cost-effective analysis studies in Singapore and beyond [44, 45]. These instruments will allow for identifying the direct costs of SKOPE and allocating costs across activities and cost centers. Unsubsidized healthcare costs of clinic/hospital visits, diagnostics, and medications will be tracked from billing records.

Qualitative data collection

The qualitative study (secondary objectives 1a and 1b) will be guided by the Theoretical Framework for Acceptability (TFA), Behaviour Change Wheel (BCW), and Theoretical Domains Frameworks (TDF) [46, 47].

TFA will focus on effective attitude, burden, ethicality, intervention coherence, opportunity cost, perceived effectiveness, and self-efficacy, and the latter framework draws on theories from implementation research and behavior change.

We will interview a purposive sample of key stakeholders at each clinic, with the option of an in-person or a remote interview. The interviews will explore the following:

1. Identify barriers, bottlenecks, and facilitators for quality CKD management (including self-management by patients)
2. Perceived acceptability of SKOPE CKD care strategy and hybrid CKD care delivery (in-person and remote consultations)
3. Impact of incorporating SKOPE on existing practice
4. Whether the SKOPE strategies affected other services by nurses and physicians in terms of efficiency, timeliness, effectiveness, patient-centeredness.

The preparedness of the patients and staff related to CKD management, especially concerning potential or existing pandemics like COVID-19 will be explored.

Interviews will be conducted at pre-implementation, 12 months, and 36 months after rolling out SKOPE. Each interview will last about 45 min to an hour.

Plans to promote participant retention and complete follow-up {18b}

Participants will work with the same intervention team whenever possible and have multiple options to schedule interview times. Before each follow-up visit, participants will be reminded of their appointment by phone call or message. If participants are unable or unwilling to visit the site, they will answer questions about their health

status by phone. The CRC will make up to three attempts to reach the participant for each scheduled follow-up, with at least 6 weeks between the first and third attempts. Participants will receive reimbursement for completing each yearly physical visit.

Data management {19}

The entire trial is performed according to the Good Clinical Practice Guideline of the International Conference on Harmonization (ICH-GCP) guidelines, and each institute will follow its own Research Data Management and IT security policy (National University of Singapore (NUS), SingHealth, NUP, and SCRI). Before initiation of the trial, CRC will be trained on properly taking consent, administering data collection forms, and entering data into REDCap. Hardcopies of forms will be checked regularly (e.g., once every week for 1 month during baseline assessment and then once a month subsequently till the end) for possible errors by auditors and sent for correction before data entry into REDCap. The REDCap has built-in features for preliminary data checks like missing data, range checks, and skipping logics during the data entry. Entered data will go through another round of verification and quality checks by the research coordinator at the clinics. The data manager from Duke-NUS Medical School will perform the final quality control assessment including the outliers and logical checks and clean data on a regular basis under the guidance of the trial statistician. Any errors, inconsistencies, and discrepancies at any stage will be resolved in a prompt manner.

Confidentiality {27}

The informed consent and documents with patient identifiers will be stored in secured places at each polyclinic, and the site PI will be responsible for the privacy and security of the patient data. Any source data or identifiable data will be accessed by the research team at sites under the oversight of site PIs.

Identifying information will not be collected anywhere on case report forms (CRFs) and REDCap. Only de-identified data will be entered in REDCap and saved for further usage by the coordinating center and the third-party vendor, who will manage and analyze the REDCap database. The de-identified data will be preserved in secured servers hosted in SCRI during the trial.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

See above 26b there will be no biological specimens collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Effectiveness analysis

The primary outcome of the rate of change in eGFR will be evaluated between the intervention and usual care arms with a linear mixed effects model, from baseline to 36 months where the slopes represent the rate of change in eGFR [36]. Randomized intervention arm, randomization stratification factors, baseline eGFR, two-way interactions of intervention by time, and other confounders if appropriate, will be included as fixed effects; intercept and time will be included as random effects with an unstructured covariance matrix for the random effects [48].

Further exploratory analysis will be performed using a two-slope linear spline mixed-effects model for eGFR to evaluate the effect of the intervention on the acute and chronic slopes separately.

Secondary outcomes related to CVD risk score, HRQoL (EQ-5D-5L), anthropometric parameters, and laboratory and clinical outcomes will be compared between the trial arms using the generalized mixed effects models for repeated measurements. The mean difference in the secondary outcomes between trial arms at each trial visit will be estimated from the models with its 95% confidence interval.

Details information on the statistical analysis will be presented in a stand-alone statistical analysis plan, which will be finalized before the database lock.

Cost-effectiveness analysis

We will model costs and effectiveness over a lifetime horizon and apply a discount rate of 3% beyond the first year according to Singapore guidelines [49]. Cost and effectiveness for the first 3 years will be accrued based on information collected during the RCT. Drawing on existing cost-effectiveness studies for CKD patients [50, 51], we will develop a Markov model to estimate the cost and effectiveness beyond the third year. We will derive the probabilities of progressing to ESKD, CVD event, and death from established risk prediction equations calculated in the last year of the RCT [32, 37]. Annual unsubsidized healthcare costs for each health state (e.g., non-dialysis, dialysis, CVD event) will be estimated in consultation with clinicians.

Budget impact analysis

For the budget impact analysis, we will estimate the incremental cost of scaling up the intervention to all eligible adults from the health ministry (public payer) perspective using established guidelines for budget impact

analysis [52–54]. Costs will be presented for the first 3 years of the scale-up assuming the intervention is able to reach all eligible adults within 2 years.

Qualitative data analysis

The interviews will be audio-recorded and translated directly into English on transcripts by an expert native bilingual speaker. Both deductive (framework-based) and inductive data analyses will be performed. Data will be managed using QSR International's NVivo 10 TM software.

Interim analyses {21b}

Two interim analyses, one at 1/3rd and another at 2/3rd of the subjects complete at least 12 months follow-up in the trial. The interim analyses will be performed to evaluate safety outcomes and fidelity measures for the Data Safety & Monitoring Board (DSMB) review. No primary or secondary effectiveness outcomes will be evaluated in the interim analyses.

Methods for additional analyses (e.g., subgroup analyses) {20b}

While randomization ensures approximate balance with respect to both known and unknown confounders, the test of intervention effectiveness will also be performed after adjustment for potential covariates including age, sex, ethnicity, baseline eGFR, and baseline ACR. Subgroup analyses for the primary and key secondary outcomes will be performed by baseline CKD stages, diabetes status, albuminuria levels, and KFRE scores.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

All analyses will be performed in accordance with the intention to treat principle. Missing data will not be imputed for outcomes collected more than once post-baseline as they will be analyzed using mixed-effects models with repeated measurements.

Plans to give access to the full protocol, participant-level data and statistical code {31c}

De-identified data will be made available 2 years after the project completion, with some restrictions due to the study's ethics approval. Interested individuals can contact the corresponding author or the SingHealth institutional review board at <irb@singhealth.com.sg>.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The trial management committee (TMC) will be chaired by the PI. Its membership will comprise of all co-PIs and polyclinic site PIs who will participate in protocol finalization (weekly or more frequent meetings). A monthly meeting will be held, after protocol finalization. The recruitment, retention, and follow-up rates of patients at each site and logistical details will be discussed. TMC will ensure timely reporting to the DSMB.

The Steering Committee will provide strategic input to different components of the project in light of the new evidence as well as policies. Annual meetings will be held. The committee will include all TMC members, leadership of the polyclinics, and representation from the Singapore Society of Nephrology, National Kidney Foundation Singapore, and HPB, Singapore. The chair of the Steering Committee will also facilitate the scale-up of SKOPE in the public sector in Singapore primarily through the Ministry of Health Office of Healthcare Transformation, HPB, and regional polyclinic clusters and health centers.

Composition of the data monitoring committee, its role and reporting structure {21a}

Although no new drugs or devices are being evaluated, a panel of DSMB comprising of four members not associated with the trial will be formed to review the data during the two planned interim analyses on all-cause mortality and hospitalizations, and CVD, as well as potential adverse effects of SGLT2i in light of pre-specified Medical Research Council (MRC) Guidelines for good clinical practice in clinical trials. A DSMB charter will also be created for the SKOPE study.

Adverse event reporting and harms {22}

Adverse events are categorized into one of several groups: angioedema and anaphylactic reaction, peripheral edema, hypotension, CHD, heart failure, stroke or transient ischemic attack, headache, dizziness or lightheadedness, flushing, cough after initiating antihypertensive medication, abdominal pain, muscle pain, falls and trauma, dialysis or kidney transplant, acute kidney injury, urinary tract infection, genital infection, gout, hyperkalemia, amputation, or other. Serious adverse events are defined as death, life-threatening events, events resulting in permanent disability, hospitalization, and prolongation of hospital stay.

The CRC will follow up with patients every 6 months to document adverse events, regardless of severity or association with the trial medications. The health coaches will also solicit adverse events 1 month from baseline and every 3 months during telephone sessions. For suspected adverse events, the CRC will complete the reporting form and inform the site PI (or designee) to start adjudication. The CRC will also share details with the Duke-NUS PI for confirmation. Adverse events will be reported by site

PI or designee to the Central Institutional Review Board (CIRB) according to its guidelines, with only related serious adverse events (SAEs) reported to CIRB.

Frequency and plans for auditing trial conduct {23}

The study monitoring plan, recruitment rate, study compliance, and findings from previous visits determine the frequency of regular and interim visits.

Plans for communicating important protocol amendments to relevant parties {25}

Protocol amendments approved by the PIs and site PIs will be submitted to CIRB before their implementation. All site PIs will be sent a copy of the revised protocol after CIRB's approval of the amendments. Modifications that affect the risks of participation and trial experiences will be communicated to study participants physically, by phone, or by email, including reconsenting of current and past participants if required by the CIRB. All amendments will be updated on ClinicalTrials.gov.

Dissemination plans {31a}

The results of the trial will be published in scientific journals and other media and shared with key stakeholders in Singapore including all study participants, administrative health officials of SingHealth, NUP, and other health-care networks, professional organizations (cardiac, nephrology, and hypertension societies) and the Ministry of Health, and presented in local, regional, and international conferences. A health policy forum will be conducted to share the key findings in Singapore and regionally. The dissemination of the results is likely to enhance the scale-up of the trial strategies.

Discussion

Our SKOPE trial aims to evaluate an innovative, multicomponent "packaged" intervention integrated into Singapore's primary care system to preserve kidney function and prevent CVD in patients with CKD.

The study's randomized design ensures an equal distribution of confounders between the intervention and usual care groups. The economic evaluation will offer policymakers valuable insights into the model's financial viability. Demonstrating a sustainable, cost-effective CKD management program that effectively reduces kidney function decline and cardiovascular risk in busy polyclinics will support scaling it across Singapore's primary-care clinics. The trial design ensures seamless integration of the intervention's four components into existing polyclinic infrastructure. Training will occur during scheduled medical education sessions and motivational conversations at work sites, and the use of SGLT2i will involve already approved agents. While health coaches will have an increased role in telephone follow-ups, existing providers will deliver the interventions without creating a parallel care system.

The SKOPE trial findings would fill a large knowledge gap, generate much-needed information on addressing health systems barriers to CKD care, and optimize the delivery of evidence-based interventions to preserve kidney function and improve cardiovascular health and quality of life in patients with CKD.

There are several additional strengthens and novel aspects of our proposal: (1) SKOPE trial builds on our extensive experience of successful implementation of SingHypertension trial in the polyclinics; (2) our SKOPE trial is unique in its selection of a combination of CKD-specific lifestyle and pharmacologic strategies for a real-world setting to optimize the benefit focused on kidney outcomes as well as CVD; (3) SKOPE intervention components are guided by stakeholder (patients) engagement (e.g., health coach, CKD specific dietary recommendations, virtual follow-ups) which will likely facilitate its success; (4) the implementation of SKOPE trial primary care systems would enhance the generalizability of the findings; (5) a hybrid care delivery approach is likely to enhance the outreach of SKOPE intervention; (6) the detailed measurements collected on process outcomes and intervention fidelity during the trial will help understand the extent to which the intervention was implemented as intended, and identify any potential gaps that need further strengthening. SKOPE would leverage the existing infrastructure in the polyclinics in Singapore and, therefore, is likely to be cost-effective and sustainable.

If shown to be effective, cost-effective, and acceptable, SKOPE intervention has the potential to become a vanguard CKD care model for preserving kidney function and cardiovascular risk reduction in patients with CKD in the primary care setting in Singapore and many other countries where the burden of CKD is rising steely. Scaling up SKOPE will lead to a 25% to 30% reduction in kidney failure and CVD (coronary heart disease, stroke, heart failure, peripheral vascular disease) related mortality. Additionally, SKOPE would lead to substantial improvement in the quality of life of patients with CKD.

In summary, this study aims to assess the effectiveness and cost-effectiveness of a multicomponent intervention for CKD patients. Successful outcomes could lead to widespread adoption, potentially improving

patient quality of life. Findings will also guide future research and clinical practices in this field.

Trial status

Study recruitment began on 21 July 2022. The current protocol version 10 is up to date as of 10 July 2023. Recruitment is anticipated to be completed by 15 Aug 2024.

Abbreviations

CKD	Chronic kidney disease
SKOPE	Strategies for Kidney Outcomes Prevention and Evaluation
ESKD	End-stage kidney disease
SGLT2i	Sodium-glucose cotransporter-2 inhibitors
DAPA-CKD	Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
CVD	Cardiovascular disease
RCTs	Randomized controlled trials
BP	Blood pressure
COBRA-BPS	Control of Blood Pressure and Risk Attenuation–Rural Bangladesh, Pakistan, Sri Lanka
eGFR	Estimated glomerular filtration rate
SKOPE	Strategies for kidney outcome evaluation and prevention
HRQoL	Health-related quality of life
BMI	Body mass index
QALYs	Quality-adjusted life-years
SHP	SingHealth Polyclinics
NUP	National University Polyclinics
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRC	Clinical research coordinator
MCI	Multicomponent intervention
MC	Motivational conversation
HBP	Health Promotion Board
KDIGO	Kidney Disease Improving Global Outcomes
NSAIDs	Non-steroidal anti-inflammatory drugs
SEA KFRE	Southeast Asia Kidney Failure Risk Equation
NICE	National Institute for Health and Care Excellence
SBP	Systolic blood pressure
ACR	Albumin-to-creatinine ratio
SPC	Single pill combination
RAAS	Renin-angiotensin-aldosterone system
CCB	Calcium channel blocker
PI	Principal Investigator
IPAQ	International physical activity questionnaire
FFQ	Food frequency questionnaire
EMR	Electronic medical records
GP	General Practitioner
ASCVD	Atherosclerotic cardiovascular disease
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
MACE	Major adverse cardiovascular events
MAKE	Major adverse kidney events
KRT	Kidney replacement therapy
CHD	Coronary heart disease
FRS	Framingham risk score
ACE	Agency for Care Effectiveness
eHIntS	Electronic Health Intelligence System
SCRI	Singapore Clinical Research Institute
IDMS	Isotope dilution mass spectrometry
ICD	International Classification of Diseases
ABC	Activity Based Costing
TFA	Theoretical Framework for Acceptability
BCW	Behaviour Change Wheel
TDF	Theoretical Domains Frameworks
ICH-GCP	Good Clinical Practice Guideline of the International Conference on Harmonization
NUS	National University of Singapore
CRFs	Case report forms
DSMB	Data Safety & Monitoring Board
TMC	Trial management committee
MRC	Medical Research Council
CIRB	Central Institutional Review Board
SAEs	Serious adverse events

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08564-1.

Additional file 1. Telephone follow-up checklist.

Additional file 2. Physician management checklist.

Additional file 3. Original funding document.

Additional file 4. Ethical approval document for initial approval.

Additional file 5. Ethical approval document for extension approval.

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Authors' contributions {31b}

THJ is the chief principal investigator. She conceived the study, led the proposal, and drafted the protocol. NCT, AGT, and the site principal investigators (PMKS, RO, BLL, KCT, ASM) contributed to modifications and adaptions in the protocol as per the local clinic workflow in each clinic. EAF contributed to the cost-effectiveness plan and MG contributed to the analytic plan in discussions with THJ. All authors read and approved the final manuscript.

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Data availability {29}

De-identified data will be made available 2 years after the project completion, with some restrictions due to the study's ethics approval. Interested individuals can contact the corresponding author or the SingHealth institutional review board at <irb@singhealth.com.sg>.

Declarations

Ethics approval and consent to participate {24}

Ethical approval (Additional files 4 and 5) has been obtained from the SingHealth Centralised Institutional Review Board for the original protocol as well as the amendments (CIRB Ref: 2022/2012). Written informed consent will be obtained prior to participant involvement in the study.

Consent for publication {32}

This manuscript does not contain individual personal data from participants. A model consent form that will be used in this study is available upon request.

Competing interests {28}

The authors have no competing financial interests to declare.

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