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Hyperkalemia prevalence, recurrence, and treatment in patients on haemodialysis in China: protocol for a prospective multicentre cohort study (PRECEDE-K)

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ABSTRACT

Introduction

Hyperkalemia (HK) is a potentially life-threatening electrolyte imbalance associated with several adverse clinical outcomes and is common in patients with kidney failure. However, there is no evidence on the occurrence, recurrence, and treatment of HK in patients on hemodialysis (HD) in China.

Methods and analysis The HK Prevalence, Recurrence, and Treatment in Haemodialysis Trial (PRECEDE-K; NCT04799067) is a prospective, multicenter, observational, cohort study being conducted across 15-18 sites in China. Approximately 600 patients with end-stage kidney disease on HD are anticipated to be enrolled and will be followed up for 24 weeks. Patients will be in the long interdialytic interval (LIDI) at enrollment and will receive follow-up care every 4 weeks in LIDI for pre-dialysis and post-dialysis (at enrollment only) serum potassium measurements. To obtain pre-dialysis serum potassium levels in the short interdialytic interval (SIDI), a follow-up visit will be performed in the SIDI during the first week. Information on concomitant medications, blood gas analysis, and biochemistry measurements will be obtained at enrollment and at each follow-up visit. The primary endpoint will be the proportion of patients experiencing HK (defined as serum potassium level >5.0 mmol/L) at the study enrollment or during the 24-week follow-up. The key secondary endpoint will be the proportion of patients experiencing HK recurrence (defined as any HK event after the first HK event) within 1 to 6 months (if applicable) during a 24-week follow-

up, including enrollment assessment.

Ethics and dissemination

This trial has been approved by Shanghai Jiaotong University School of Medicine, Renji Hospital Ethics Committee (2020-040). The findings of this study will be disseminated through peer-reviewed publications and conference presentations.

Key words: dialysis, end-stage renal failure, epidemiology

Article summary

Strengths and limitations

- The PRECEDE-K trial will be the first prospective multicentre cohort study with a large sample on the prevalence, recurrence, and treatment pattern of HK in patients with HD in China.
- The PRECEDE-K trial will providing high-quality evidence and meaningful insights for guiding physicians in to clinical practice.
- However, the PRECEDE-K trial will not analyze neither the prognosis nor the impact on cardiovascular events of HK.

Background

The prevalence of end-stage renal disease (ESRD) is on the rise globally. In 2010, 2.618 million patients with ESRD received renal replacement therapy (RRT) worldwide and its use is projected to be more than double by 2030, with the highest prevalence in Asia.[1] Hemodialysis (HD) is the dominant treatment modality for those who are under RRT in China. According to the Report of Chinese National Renal Data System

(CNRDS) in 2018, there were >1.3 million patients with ESRD in China, among whom there were 580,000 patients who were on HD.

Hyperkalemia (HK) is a potentially life-threatening electrolyte imbalance, typically defined as a serum potassium concentration >5.0 mmol/L[2]. Due to its detrimental effects on cardiac electrophysiology and neuromuscular function, HK has been proved to be associated with several adverse clinical outcomes, including significant arrythmia, hospitalization and associated length of stay, and all-cause mortality[3-5]. HK is common in patients with kidney failure due to diminished renal potassium excretion, with a prevalence of 30% to 50% in patients with ESRD under maintenance HD worldwide, and is recognized as a risk factor for sudden death and all-cause mortality in patients on HD[6, 7]. Chinese patients with ESRD have different spectrum of chronic kidney disease (CKD)[8], and different dietary style and treatment patterns[9], thus they may have distinct characteristics of HK occurrence and recurrence. Besides, abnormalities of potassium, rapid changes in potassium concentrations during the HD session have been suggested as a potential cause of cardiac arrhythmia.[10-13]

However, there is no evidence on the occurrence, recurrence, and the treatment of HK in patients undergoing HD in China. Meanwhile, there is no Chinese guidelines on HK management in patients undergoing HD. In the present study, we aimed to evaluate the prevalence and recurrence of HK in Chinese patients on HD and to understand the treatment pattern of HK in China.

Methods

Design

This is a prospective, observational, cohort study, which was registered with the ClinicalTrials.gov prior to initiation of patient enrollment (ClinicalTrials.gov identifiers: NCT04799067; Version 1.0; Date 12 Oct, 2020).

Patients will be in long interdialytic interval (LIDI) at enrollment visit 1 (V1). Demographic characteristics, medical history, etiology of ESRD, concomitant medications, dialysis vintage, an electrocardiogram, a pre-dialysis K^+ measurement and a post-dialysis K^+ measurement, blood routine, blood gas analysis, and other blood biochemistry measurements will be obtained. Potassium measurements, including pre-dialysis potassium measurements at the LIDI once every month (V3-V8), pre-dialysis potassium at short interdialytic interval (SIDI) during the first week (V2) for patients in HD thrice a week specifically, will be performed. Information on concomitant medications, blood routine, blood gas analysis, and other blood biochemistry measurements will also be obtained.

LIDI is defined as the interval between dialysis ≥2 days, while SIDI is defined as the 1-day interval between dialysis. For patients receiving HD thrice weekly, there will be one LIDI and two SIDI every week. For patients receiving HD twice a week, there will be two LIDIs every week.

The illustration of the proposed study design is shown in Figure 1 (patient on HD thrice a week as an example). The detailed study plan of the PRECEDE-K trial is shown in Table 1.

Figure 1. The study design of the PRECEDE-K trial

*For patients receiving HD thrice a week, V2 could be at D3 or D5 for collecting pre-dialytic serum potassium at SIDI. For patients receiving HD twice a week, visit 2 will be waived as there is no SIDI for these patients; thus, there are 7 visits in total.
**Time window is ± 1 week.

d, day; ESRD, end-stage renal disease; LIDI, long interdialytic interval; SIDI, short interdialytic interval; V, visit; w, week

Table 1. The Study Plan of the PRECEDE-K Trial

	Visit 1	Visit 2	Visit 3-8
	1d (LIDI)	3/5d [a](SIDI)	4-24 w[b] (LIDI)
ICF	X		
Screen inclusion and exclusion criteria	X		
Demographic characteristics	X		
Medical history	X		
Etiology of ESRD	X		
Vascular access	X		X
Height (cm)	X		
Pre-dialysis weight (kg)	X	X	X
Post-dialysis weight (kg)	X	X	X
Vital signs	X	X	X
Physical examination	X	X	X
Pre-dialysis serum K^+ [c] mEq/L	X	X	X
Post-dialysis serum K^+ [c] mEq/L	X		X*
Dialysis adequacy[d]	X		Evaluated at week 12
Dialysis frequency	X		X
Dialysis prescription	X		X
ECG[e]	X		X*
Echocardiography[f]	X*		X*
Urine 24-hour volume (litres)[g]			Evaluated at week 4 or week 8
Urine biochemistry measurements[g]			Evaluated at week 4 or week 8
Blood routine	X		X
Biochemistry measurements	X		X
Blood gas analysis	X		X
Concomitant medication	X	X	X

Vital signs, physical examination, pre-dialysis K^+, pre-dialysis weight, blood routine, biochemistry measurements should be collected within 30 minutes before initiation of HD. Post-dialysis weight, post-dialysis K^+ and post-dialysis BUN should be collected within 30 minutes after HD procedure.

All blood samples will be measured at local laboratory.

d, day; ECG, electrocardiogram; ESRD, end-stage renal disease; ICF, intracellular fluid; LIDI, long interdialytic interval; SIDI, short interdialytic interval; w, week;

[a]For patients receiving HD thrice a week, there are 2 SIDI in an HD section, so visit 2 can be on day 3 or day 5. For patients receiving HD twice a week, visit 2 will be waived, as there is no SIDI for these patients.

[b]Time window is ±1week.

[c]Blood samples for the determination of pre-dialysis serum K^+ concentration and post-dialysis serum K^+ concentration will be drawn before and after the HD procedure according to the routine clinical practice.

[d]Dialysis adequacy will be evaluated by URR. . To calculate the URR, post-dialysis BUN will be tested on day 1 and week 12.

[e]ECG: evaluated within 1 day before or after the enrollment in principle; allow individual adjustments in each center. All ECGs during the follow-up should be recorded in eCRF. For patients who experience HK during the study period, it is recommended to conduct at least one more pre-dialysis ECG at LIDI.

[f]Echocardiography: evaluated echocardiography data if it is conducted within 2 weeks before or after visits in principle; allow individual adjustments in each center.

[g]Urine will be collected for a period of 24 hours at either week 4 or week 8. The volume and biochemistry measurements of the 24-hour urine sample will be measured.

Study sites and period

This study will utilize primary data collected by investigators from approximately 15-18 sites in China. Patients with ESRD on HD treatment will be enrolled and will be followed up for 24 weeks.

Population

This study will include approximately 600 patients with ESRD (aged ≥18 years) receiving HD treatment twice a week or thrice a week. Patients will be eligible to be included in the study only if all of the following criteria are applicable: (1) patients are aged ≥18 years at the time of signing the informed consent; (2) patients with ESRD and on HD; (3) the HD treatment frequency is ≥2 sessions per week; (4) capable of giving

signed informed consent.

Patients will be excluded from the study if any of the following criteria are applicable: (1) acute kidney injury; (2) expected to receive renal transplantation within 6 months; (3) intracranial hemorrhage or elevated intracranial pressure within 1 month before enrollment; (4) a traumatic experience that cannot be corrected by drugs within 1 month before enrollment; (5) failure to establish vascular access; (6)has been receiving peritoneal dialysis; (7) not suitable for this study as judged by the investigators

Procedures for Withdrawal/Discontinuation

Eligible patients will be followed for up to 24 weeks, or up till occurrence of any of following events, whichever occurred earlier.

1. Death
2. End of study period
3. Loss to follow-up: defined as transfer to HD centre(s) not in this study, or refused to continue follow-up, or cannot be contacted by phone calls for three times
4. Change modality of RRT (peritoneal dialysis or renal transplantation)
5. Withdrawal of ICF
6. Investigators consider it necessary for the subjects to terminate the study

Primary outcome

The primary outcome will be proportion of patients experiencing HK (defined as serum potassium levels >5.0 mmol/L) at the study enrollment or during a 24-week follow-up.

Secondary outcomes

- The proportion of patients experiencing HK recurrence (defined as any HK event after the first HK event) within 1, 2, 3, 4, 5, or 6 months (if applicable) during a 24-week follow-up including the enrollment assessment. An HK event is defined as

any serum K^+ concentration >5.0 mmol/L within an interdialytic interval, which is usually 2 to 3 days.

- The proportion of patients with 2, 3, 4, 5, and ≥6 events of HK during a 24-week follow-up including the enrollment assessment.
- Intradialytic potassium shift (defined as the difference between pre- and post-dialysis K^+ concentration) at LIDI during the first week after patient enrollment
- Serum K^+ concentration at LIDI and SIDI in patients receiving HD thrice a week during the first week after patient enrollment.
- The proportion of patients with HK treated with any potassium binders including sodium polystyrene sulfonate (SPS), calcium polystyrene sulfonate (CPS), or sodium zirconium cyclosilicate (SZC), and specific proportion of each potassium binder, respectively, during the 24-week follow-up period.
- The proportion of HK events treated with any potassium binders including SPS, CPS, or SZC among total number of HK events during the 24-week follow-up period.
- Mean daily dose of SPS, CPS, or SZC in patients treated with any potassium binder.
- Duration of the treatment of SPS, CPS, or SZC in patients treated with any potassium binders.

Exploratory endpoints

- Risk factors for experiencing any HK (defined as serum potassium level >5.0 mmol/L) at the study enrollment or during a 24-week follow-up.

- Risk factors for experiencing HK recurrence during a 24-week follow-up.

Statistical analysis principles

Statistical methods will be primarily descriptive in nature. For categorical data, the frequency and percentage of patients in each category will be presented. Percentages will be based on non-missing data unless otherwise specified. For continuous data, descriptive statistics will be presented as the number of patients (n), mean, standard deviation (SD), median, minimum and maximum. All successfully enrolled subjects fulfilling inclusion/exclusion criteria will be included in the Full Analysis Set (FAS), which will be the primary analysis set for all primary and secondary analyses unless specified otherwise.

Primary analysis

The proportion of patents experiencing any HK at the study enrollment or during a 24-week follow-up will be presented by the percentage as well as its 95% confidence interval. HK is defined as K^+ >5.0 mmol/L while the same summary will be generated using a higher threshold of HK as K^+ >5.5 mmol/L as well, as sensitivity analysis. The proportion of patients experiencing serum K^+ concentration >6.0 mmol/L, 6.5 mmol/L, 7.0 mmol/L, and 7.5 mmol/L will be reported as well.

Secondary analysis

1. The proportion of HK recurrence within 1, 2, 3, 4, 5, or 6 month(s) after the first HK

and the proportions of patients with 2, 3, 4, 5, and ≥6 times of HK events during the 24-week follow-up will be presented using the percentage and its 95% confidence interval. The HK recurrence is defined as any consecutive HK events. An HK event is defined as any serum K^+ concentration >5.0 mmol/L within an interdialytic interval, which is usually 2 to 3 days. A higher threshold of HK event as serum K^+ concentration >5.5 mmol/L will be utilized to generate similar summaries, as sensitivity analyses.

2. Intradialytic potassium shift is evaluated by the mean difference between pre- and post-dialysis serum K^+ concentration during the first week after patient enrollment. If there are more than one serum K^+ concentrations before or after HD, intradialytic potassium shift will be the difference between the last serum K^+ concentration measurement before HD and the first serum K^+ measurement after HD. Summary statistics will be provided using mean, median, SD, minimum, and maximum. The number of subjects and the missing number of subjects will also be presented.

3. Serum K^+ concentration at LIDI and SIDI as well as the difference between LIDI and SIDI during the first week after patient enrollment will summarized with the same method as described above. This analysis will only be applicable on patients receiving HD thrice a week. LIDI is defined as the interval between dialysis (≥2 days), whereas SIDI is defined as the 1-day interval between dialysis.

4. Treatment pattern for HK with potassium binders will be assessed by: the proportion of HK patients treated with any potassium binders including SPS or CPS or SZC during the 24-week follow-up period. The proportion of patients with HK treated with specific

potassium binder including SPS, CPS, and SZC, respectively, during the 24-week follow-up period; the proportion of HK events treated with any potassium binders including SPS, CPS, or SZC among total number of HK events during the 24-week follow-up period; the mean daily dose of SPS, CPS, or SZC in patients treated with any potassium binder; the duration of the treatment of SPS, CPS, or SZC in patients treated with any potassium binder, above the categorical and continuous variables will be analyzed based on previously mentioned descriptive methods, as associated summary statistics, will be presented. Where for proportion, the denominator will always be the number of subjects in FAS.

Exploratory analysis

Univariate and multivariate logistic regression will be used to explore the association of risk factors with any HK occurrence and recurrence. HK occurrence is defined similar to that mentioned in the primary analysis, where patients experience any HK (defined as serum potassium >5.0 mmol/L) at the study enrollment or during a 24-week follow-up. The HK recurrence is defined similar to that mentioned in the secondary analysis, where patients experienced any HK event after the first HK event will be counted as with recurrence. An HK event is defined as any serum K^+ concentration >5.0 mmol/L within an interdialytic interval, which is usually 2 to 3 days. Risk factors including dialysis frequency, dialysate potassium, dialysis vintage, treatment of HK, medical history of special interest, including history of atherosclerotic heart disease, congestive heart failure, diabetes, hypertension, dialysis adequacy (URR), urine volume, and so on. Odds ratio and 95% confidence interval estimation of each risk

factor (both un-adjusted and adjusted) will be presented with 2-sided *P*-value provided.

Sample size and power calculations

The primary endpoint will be the proportion of patients experiencing HK anytime at enrollment and during a 24-week follow-up, the previously reported proportion of patients experiencing HK is 73.8% during a 2-year follow-up[9] and 58% during a 4-month follow-up.[11] In this study, an assumption is made that the proportion of patients experiencing HK will be between 58% and 73.8% during a 24-week follow-up. Precision estimates for primary endpoint under different sample sizes are presented in table 2. We assumed that 600 patients will provide a precision (half width of 95% confidence interval) estimate of 3.5% to 3.9%.

Table 2. Precision estimates for primary endpoint under different sample sizes

HK Proportion	Sample Size	Precision	95% Confidence Interval Estimate
58.0%	600	3.90%	[54.1%, 61.9%]
73.8%	600	3.50%	[70.3%, 77.3%]

HK, hyperkalemia

Data statement

All Data will be collected and entered into the electronic case report form (eCRF). The investigator will be responsible for ensuring that the required data is collected and entered into the eCRF.

Ethics and dissemination

This trial has been approved by Shanghai Jiaotong University School of Medicine, Renji Hospital Ethics Committee (2020-040). Other participating sub-centers must also

obtain ethics committee approval documents prior to the start of clinical trials. The Good Clinical Practice(GCP) regulations shall be strictly followed during the test implementation.This trial has been registered with the Chinese Clinical Trial Registry (http://www.chictr.org.cn/index.aspx) at 22 Jan. 2020. Amendments to the protocol will be reviewed by Ethics Committees. Informed consent will be obtained before collecting any patient data and patient information. The findings of this study will be disseminated through peer-reviewed publications and conference presentations.

Quality Control

The activities for quality control could include but are not limited to:

Contacts with the sites to

- Provide information and support to the investigator(s)
- Confirm that the research team is complying with the protocol and that data are being accurately recorded in the eCRFs
- Ensure that the subject ICFs are signed and stored at the investigator's site
- Ensure that the eCRFs are completed properly and with adequate quality.

Monitoring activities for:

- Checking of ICFs
- Checking that subjects exist in medical records

The extent and nature of monitoring will be decided during the study planning based on design, complexity, number of subjects, number of sites, etc.

Different signals (eg, high rejection rate in a site) should be used as potential identification of low protocol compliance by investigators.

If these or any other signal occurs or if the investigator is suspicious of a potential non-optimal level of protocol compliance by the site investigator, specific measures should be adopted to evaluate the situation, identify the issue and implement specific action plans to correct the situation.

Training of Study Site Personnel

The Principal Investigator will ensure that appropriate training relevant to the Observational Study is given to investigational staff.

Patient and Public Involvement

No patient involved.

Discussion

HK is common in patients with kidney failure due to diminished renal potassium excretion despite the widespread and dynamic prescription of low-K^+ dialysis baths and K^+ binders. According to a prospective multicenter study in France, the percentage of patients with long-term HD experiencing HK at any time was 73.8% (K^+ >5.1 mmol/L), 57.9% (K^+ >5.5 mmol/L), and 34.5% (K^+ >6 mmol/L).[14] Another large retrospective study analyzed data derived from the United States Renal Data System (USRDS), reported that HK prevalence was consistently estimated at 16.3 to 16.8 events per 100 patient-months.[15]

Recently, an epidemiological study reported that the prevalence of HK in Chinese outpatients is 3.86%, and the prevalence of hyperkalemia in patients with CKD increased to 22.89%.[16] However, there is no high-quality evidence on the epidemiology of HK and no Chinese guidelines on the management of HK in Chinese patients on HD. The PRECEDE-K trial will evaluate the prevalence of HK in Chinese patients on HD.

Previously, acute HK was considered as a fatal complication, however, with the deepened understanding of HK, emphasis have changed from acute HK to chronic HK in the recent years. Acute HK management involves cardiac monitoring, acute medical

interventions, or possibly dialysis. However, chronic HK requires ongoing management to correct the underlying disturbances in potassium balance including nonpharmacological and pharmacological interventions.[17] A higher rate of HK recurrence was observed 1, 2, and 3 months after an HK occurrence (eg, 35.6% of HK cases with K^+ >6 mmol/L within 3 months after an initial HK of the same magnitude) in hepatic hemosiderosis in maintenance hemodialysis (MHD) patients despite widespread prescription of low-K^+ dialysis baths and K^+ binders)[14]. Therefore, the proportion of patients experiencing HK recurrence is an important secondary outcome in this current study.

Compared with pre-dialysis K^+, post-dialysis K^+ is rarely investigated, and so its acceptable range remains unknown. Based on the difference between dialysate and serum potassium levels, serum potassium levels drop significantly after HD, and 45% of patients present with post-dialysis hypokalemia of <3.5 mmo/L in previous study.[18-20]Based on a cohort study of 3967 participants on MHD from the Dialysis Outcomes and Practice Patterns Study (DOPPS) in Japan (2009-2012 and 2012-2015) compared with post-dialysis potassium levels 3.0 to <3.5 mEq/L, the hazard ratios of post-dialysis hypokalemia (<3.0 mEq/L) were 1.84 (1.44-2.34) in the unadjusted model, 1.44 (1.14-1.82) in the model without adjusting for pre-dialysis serum potassium levels, and 1.10 (0.84-1.44) in the model adjusted for pre-dialysis serum potassium levels. This research suggested that post-dialysis hypokalemia was associated with mortality, but this association was not independent of pre-dialysis potassium.[21] Therefore, we regarded intradialytic potassium shift (defined as the difference between pre- and post-dialysis

K^+) as a secondary outcome in our research.

A retrospective study reported that the prevalence of HK on the day after the LIDI was 2.0 to 2.4 times as high as on the day after the SIDI in patients with MHD.[15] The LIDI was reported as a time of heightened risk among patients receiving HD. [22] Serum K^+ levels at LIDI and SIDI in patients receiving HD thrice a week during the first week after patient enrollment was another secondary outcome.

The development of HK is usually the result of a combination of factors superimposed on comorbidities (eg, diabetes mellitus, advanced stages of heart failure), use of potassium-based salt substitutes, and use of medications interfering with potassium homeostasis-like angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), aldosterone receptor antagonists, β-blockers, and others [23]. Considering the potential risk factor of HK, we will record all the comorbidities and drugs in this study for further exploration.

Compared with the reference group of serum potassium level of 4.0 to 5.0 mEq/L, higher serum potassium level (5.6-6.0 mEq/L) was associated with mortality in adjusted analysis (HR: 1.13, CI:1.06-1.20), and higher serum potassium levels (>6.0mEq/L) was associated with arrhythmia composite (includes sudden death or arrhythmia-related hospitalizations) in adjusted analysis (HR: 1.21, 1.05-1.38).[3] Continuous rhythm monitoring was performed using the remote-monitoring capability of the implantable loop recorder device in patients undergoing HD at 8 centers.[24] In multivariate survival frailty analyses, a higher risk for conduction disorder was associated with plasma

potassium levels >5.0 mmol/L. Further understanding and management of HK will benefit the survival in MHD patients.

Conclusion and clinical implications

PRECEDE-K will be the first prospective study on the prevalence, recurrence, and treatment pattern of HK in patients with HD in China, which will provide comprehensive data of the disease prevalence, recurrence, and treatment patterns for HK in patients with HD in China. The results obtained will provide meaningful insights for guiding physicians in to clinical practice. We hope the results obtained in this study will provide better perspectives and a high-quality evidence on the occurrence, recurrence, and treatment of HK in patients on HD.

Conflict of Interests

The PRECEDE-K Trial was supported by AstraZeneca Investment China Co Ltd, Shanghai, China.

Funding

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Contributorship statement

Principal investigator(PI), Zhaohui Ni; sub-PI and writing, Haijiao Jin; sub-PI, Renhua Lu, Li Zuo, Weimin Yu, Junsheng Wang, Rong Wang, Yuqing Ren, Qiongqiong Yang, Jie Xiao, Qinghong Zhang, Lihong Zhang, Xinzhou Zhang, Qinkai Chen, Chaosheng Chen, Guojian Shao, Qun Luo, Li Yao, Shuguang Qin and Hui Peng; executive, Qing Zhao; methodology, Shirley Shang.

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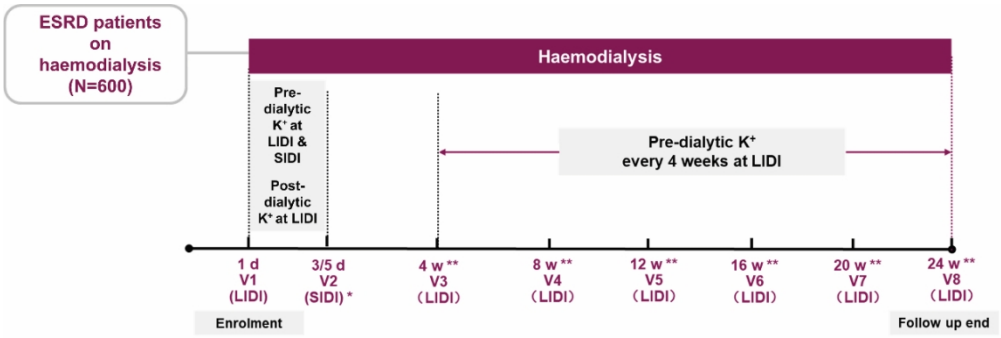

Figure 1. The study design of the PRECEDE-K trial

370x124mm (87 x 87 DPI)

STUDY INFORMATION AND INFORMED CONSENT FORM

There are [4] parts to this document:

Part I: the "**Study Information**" essential to your decision to take part in the clinical study.

Part II: the "**Future Research Information**" which explains the possibility to contribute to future research.

Part III: your "**Consent Form**" which summarise what you may agree to.

Part IV: supplementary information in the "***Additional information for patients***" Section.

PART I: STUDY INFORMATION

[Study number D9480R00033]

Title of study: Hyperkalaemia Prevalence, Recurrence and Treatment in Haemodialysis: A prospective multi-centre cohort study

Dear Madam/Sir,

You are invited to take part in this study because you are diagnosed with end stage renal disease (ESRD) and is on haemodialysis (HD). Participation requires your written consent. Before you decide whether you want to participate in this study, you will be given an explanation about what the study involves.

The overall description of this study has been reviewed by an independent Ethics Committee to ensure that the rights, safety and well-being of study patients are protected.

Your condition may not improve if you join the study. But, the information we get from this study might help other patients with the same condition in the future.

1 What is this study about?

We are doing this study to learn more about occurrence and recurrence of hyperkalaemia（HK） in Chinese HD patients and to understand the treatment pattern of HK in China and also to better understand the risk factors associated with HK.

About 600 people from approximate 15 hospitals will take part in this study.

2 Do I have to take part?

You have a choice whether or not you would like to participate.

Please take as much time as you need to make a decision about whether or not you would like to participate in this study. It may be helpful to talk with your friends and family as you make this decision.

If you join the study, you can leave at any time (see “section 10” for more details). Leaving will not affect your care. If you choose to leave the study, please let your study doctor know as soon as possible.

If you don’t join the study, you will continue to receive care for your disease. Your study doctor or treating physician will talk to you about other possible treatments, their risks and benefits.

3 What will happen if I join the study?

Because this is an observational study, no medications or other treatments are provided to you by the Sponsor as part of this study.

You will continue to come for your routine doctor’s appointments and to take your regular medication as prescribed by your doctor.

You will be in the study for about 6 months.

During the visits, information will be collected for the study and this might add some extra time to your routine visit of approximately 10 minutes.

If you cannot come to a visit, you must tell your study doctor.

Please note that the study, and your participation in the study, may be stopped earlier than expected, for example for scientific or safety reasons (see “section 6” for more details).

4 What are the required tests and procedures?

To conduct the study, some tests and procedures will have to be performed on you.

In addition to the standard of care examinations for the disease the following tests and procedures will be included:

- **Enrolment(Day 1, 1 visit)**: You will be in Long interdialytic interval (LIDI) at enrolment.

  ✓ Demographic characteristics

  - Your general information such as age, gender and race will be collected.

  ✓ Medical history, Etiology of ESRD

  - Your study doctor will collect information about your medical history (history of previous disease and surgery history) and the cause of ESRD.

  ✓ Clinical evaluations and laboratory tests

  - Clinical evaluations, which include vascular access, physical examination, height, pre-dialysis and post-dialysis weight, electrocardiography (ECG), echocardiography(not mandatory), blood pressure, pulse, heart rate will be performed.
  - You blood will also be tested for pre-dialysis and post-dialysis serum K+, pre-dialysis BUN and post-dialysis BUN, Blood routine, Biochemistry measurements, Blood gas analysis.
  - Dialysis prescription and frequency will be collected. Dialysis adequacy will be evaluated.

  ✓ Concomitant medication

  - Any medication used by you while participating in this study will be collected for dosage, duration and mode of administration.

- **Follow-up(24 weeks, 7 or 8 visits)**: You will be in short interdialytic interval (SIDI) at visit 2 (if applicable) and in LIDI at visit 3-8.

  Visit 2(Only applicable for HD received thrice a week)

  ✓ Clinical evaluations and laboratory tests

  - Clinical evaluations, which include physical examination, pre-dialysis and post-dialysis weight, blood pressure, pulse, heart rate will be performed.
  - You blood will also be tested for pre-dialysis serum K+.

✓ Concomitant medication

- Any medication used by you while participating in this study will be collected for dosage, duration and mode of administration.

Visit 3-8

✓ Clinical evaluations and laboratory tests

- Clinical evaluations, which include vascular access, physical examination, pre-dialysis and post-dialysis weight, electrocardiography (ECG, not mandatory), echocardiography(not mandatory), blood pressure, pulse, heart rate will be performed when you visit the study site according to the study schedule.
- You blood will also be tested for pre-dialysis and post-dialysis serum K+(not mandatory), pre-dialysis BUN and post-dialysis BUN, Blood routine, Biochemistry measurements, Blood gas analysis when you visit the study site according to the study schedule.
- Dialysis prescription and frequency will be collected, and dialysis adequacy(evaluated at V5) will be evaluated at each visit.
- Urine 24- hour volume and biochemistry measurements will be performed at V3 or V4.

✓ Concomitant medication

- Any medication used by you while participating in this study will be collected for dosage, duration and mode of administration at each visit.

The complete list of tests and procedures, including their detailed schedule is available in “part 4: Additional Information for Patients”.

5 What are the risks and possible benefits of joining the study?

There is no immediate clinical benefit for you, however the information we get from this study may help us to describe how HD patients with HK are managed in real-life practice, and to increase our knowledge about the disease and its symptoms. This will hopefully help us to better treat HD patients with HK in the future.

Since the study is observational, it will not change how your disease is managed by your doctor. There are no physical risks of taking part in this study.

6 What happens if something changes while I am in the study, e.g., if new information is found?

Changes may happen in the study that could make you change your mind about continuing to take part. If something changes, we will tell you as soon as possible.

You can choose to leave the study at any time. For more details see section 10 below.

The study doctor can also choose to take you out of the study if they believe that it is best for you.

Your participation in the study also stops when the Sponsor, health authorities, the ethics or regulatory agencies decide that the study must be stopped.

7 What happens if I am harmed or injured during the study?

If you become ill or are injured while you are in this study, you must tell your study doctor straight away.

Injuries that have been caused by the study tests or procedures are called 'research injuries'. Injuries caused by your usual medical care or your disease, are not research injuries.

The Sponsor has an insurance to cover the costs of research injuries as long as you have followed your study doctor´s instructions. Sponsor will pay the costs of medical treatment for research injuries, provided that the costs are reasonable, and you did not cause the injury yourself.

8 What will happen to my data gathered in the study?

a. Which data are collected?

In order to conduct the study, the Study site will have to collect and register information about your identity (such as your name, address, telephone number) as well as data that is necessary to assess your health conditions, your medical condition and medical history (this may include information from your physicians/ available in your medical records), your demographics (age, gender, *ethnic*).

b. What are my data needed for?

Your data are needed to better understand the studied disease and associated health problems and publish research results in scientific journals or use them for educational purposes.

c. Who can access my data?

Only at the study site, your name and contact details will be accessible to the study doctor and the study team to conduct the study. Non-medical personnel acting on behalf of the sponsor and being bound by a duty of confidentiality as well as Health authorities and Ethics Committees may also be given access to this data only to verify that the study is carried out in compliance with legal and quality requirements.

The study site will share your data with the sponsor but only after they have been coded (which means that your name, contact details have been replaced by a code). The sponsor may share your coded data with its Research partners and Service providers for the purposes of a drug development programme.

In order to ensure proper conduct and accurate results of the study the sponsor will share your coded data with authorities and possibly with Ethics Committees. They may also be shared with scientific journals, so the study results can be reviewed by independent scientists and to ensure the accuracy of results.

In **none** of these cases your identity will be revealed.

Some of the above-mentioned persons may be located outside your country. If this other country does not have equivalent personal data protection standards than your country, appropriate Safeguards (such as contracts and technical Security measures) will be adopted to protect and maintain the confidentiality of your data.

d. How long will my coded data be kept?

The study site and the sponsor are obliged to keep all study data for a number of years to comply with study site's and Sponsor's legal obligations. You can find out more about how the sponsor keeps personal information at www.astrazenecapersonaldataretention.com. Your coded data will then be deleted or anonymised.

e. What are my rights under data protection law?

Subject to local laws, *y*ou have the right to review which of your data are collected and being used;

To ensure the scientific integrity of the study, you will not be able to review some of the data or receive a copy of it until the study ends.

f. What does anonymised data mean?

Health authorities as well as pharmaceutical companies believe that access to clinical studies data advances clinical science and medical knowledge and is in the best interest of patients and public health, provided that patient privacy is protected. Therefore, the

sponsor may generate and share internally or with other researchers an anonymised set of your data collected in the study (e.g., on www.clinicalstudydatarequest.com). This means your coded data will be stripped of your Patient code as well as of any other information that could reasonably be used to identify you such as your date of birth.

9 What are the costs of taking part?

Participating in this study will not cost you anything more than the costs related to your routine appointments with your doctor. You will not be paid for being in this study.

You may be reimbursed for reasonable expenses incurred due to your participation in the study (for example: travel). If so, you will be paid RMB 150 per visit per protocol.

10 What will happen if I want to quit the study?

Your participation in the study is voluntary which means you can stop your participation at any time. If you want to stop your participation, you should tell the study doctor.

If you stop participating in the study, the study doctor will stop the collection of your data but your previously collected data will be kept and used to guarantee the validity of the study and comply with regulatory requirements, as allowed by law. The study doctor will then invite you to have an end of study examination to check your wellbeing. If you don't show up at a planned visit, the study doctor will try to reach you. If the study doctor cannot reach you, public sources will be consulted to verify your wellbeing. This is important for study results. It is not mandatory but would be helpful for the study if you explain to your study doctor why you wish to stop your participation, in particular if you have experienced discomforts.

If you would like your data not to be used after you quit the study, you must inform the study doctor. In such case, your coded data previously collected will be kept as required by clinical regulations.

11 Who can answer any questions I may have?

<Name of ethics committee (EC)> has reviewed the plans for this study to make sure that people who take part in this study are protected from harm.

If you have any questions about your rights during your taking part in this study, you can contact:

< Provide contact name, phone number and address of for EC >

If you have any questions about the study, please contact:

Study doctor <*insert details*>	Study Coordinator (e.g. nurse appointed to the study) <*insert details*>
Phone No. <*insert details*>	Phone No. <*insert details*>
Address <*insert details*>	Address <*insert details*>

12 How to find out more after the study?

Information about this study will be posted on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov. These websites do not contain any information about you. You can visit this website for more information. You may also get other information about your participation in the study from Sponsor via your study doctor.

PART 2: FUTURE RESEARCH INFORMATION

In addition to participating in the study, we would like to know if you would be willing that your coded data are used in future research projects with appropriate ethical approval.

You are free to consent to the use of your coded data for future research. If you decide not to do so, you may still take part in the clinical study.

1 What is future research?

Future research is important to advance science and public health. At present, however, it is not possible to foresee all details of future scientific research projects. These future scientific research projects are beyond the scope of the study and use of data as outlined in part 1 and may occur whilst the study is ongoing or after the study has finished.

Your coded data may only be used for scientific health-related research to find new ways to detect, treat, prevent or cure health problems.

They may also be used jointly with information from other sources outside typical clinical research settings, e.g. from public research databases. However, they will not be combined with other information in a way that could identify you. Your coded data and may also be anonymized for some of the future scientific research.

2 May my coded data be shared?

The sponsor may share your coded data with research partners. This may include researchers from research hospitals, and companies.

Some of the above-mentioned recipients may be located outside your country. The data protection laws which apply in those countries may not be as stringent as the laws in your country. Nevertheless, appropriate safeguards and security measures will be taken in order to protect and maintain the confidentiality of coded data.

3 How will my privacy be protected?

Your coded data will be subject to appropriate safeguards, and will only be used for the purpose of scientific health related research. They will not be used to contact you or to affect your care or any other decision affecting your life such as insurance rates or employment opportunities.

4 What if I want to withdraw from future research?

Your participation in future research is voluntary. You are entitled to withdraw your consent for future research at any time, without giving a reason and without a negative effect on your standard of medical care. If you wish to withdraw, please inform your study doctor.

You may still continue to participate in the research study even if you choose to withdraw from future research.

If you withdraw from future research, your coded data will not be used for future research. Your coded data (either copied from the research study database or newly generated) will also be destroyed unless this information is already included in analyses or used in scientific publications or if the coded data been anonymized and therefore we can't identify your data.

5 Results from Future Research?

We may have to study coded data from many people over many years before we can know if the results of future research are meaningful.

Therefore, you should not expect to receive individual results from future research projects. We will not give any such data to your doctor and we will not put them in your medical record as they are not individual valid results.

You are free to consent to the use of your coded data for FUTURE RESEARCH. If you disagree, you can indicate this in the CONSENT FORM.

PART III: CONSENT FORM

Study Code:	D9480R00033	Site No:	
Sponsor:	AstraZeneca China	Investigator:	
Study Title:	Hyperkalaemia Prevalence, Recurrence and Treatment in Haemodialysis: A prospective multi-centre cohort study		

I confirm that:

- The study doctor or study personnel delegated by the study doctor has explained the study to me comprehensively.
- I have had the opportunity to discuss the study with the study doctor and all my questions were answered.
- I have had an adequate amount of time to consider the study.
- I have read and understood all the above information related to the study.
- I understand that I will receive a copy of this document once I have signed it.
- I understand that my decision to take part in the study is entirely voluntary. If I decide not to participate in the study or to stop my participation during the study, this will not affect my standard medical care.
- I have truthfully answered all questions about my medical history and will follow all rules listed in the document.

I consent to take part in the research study and study procedures described herein. I understand that my participation also entails:

- My name and contact details being collected during the study as described to me, and accessed and reviewed by listed authorised people;
- My coded data being used by the sponsor or by people or companies acting on its behalf or working with the sponsor;
- My coded data being used by persons or organisations located in countries that do not have data protection rules equivalent to those of my country. I understand that the sponsor monitors these uses and takes all possible measures to protect my privacy;

SIGNATURE CONSENT FORM

Signature of participant	Date of Signature
Printed name of participant	
Signature of person conducting the informed consent discussion	Date of Signature
Printed name of person conducting the informed consent discussion	

Please complete the following if legally accepted representative or impartial witness is applicable.

Signature of legally accepted representative	Date of Signature
Printed name of legally accepted representative	
Relationship of legally accepted representative to participant	
Signature of impartial witness	Date of Signature
Printed name of impartial witness	

When signed and dated, we will give you a copy of this form.

PART IV: ADDITIONAL INFORMATION FOR PATIENTS

1 Sponsor details:

Sponsor details	Sponsor: AstraZeneca Investment (China) Co., Ltd, No.199 Liangjing Road Shanghai 201203, China The sponsor has the overall responsibility for the research study.

2 Detailed list of visits and Test/Procedures

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	day 1	day 3 or 5	week 4	week 8	week 12	week 16	week 20	week 24
Pre-dialysis serum K^+	X	X	X	X	X	X	X	X
Post-dialysis serum K^+	X							
Pre-dialysis BUN & Post-dialysis BUN	X				X			
Blood Sample Collectionroutine	X		X	X	X	X	X	X
Blood Biochemistry measurements	X		X	X	X	X	X	X
Blood gas analysis	X		X	X	X	X	X	X
Urine 24- hour volume & Urine samplebiochemistry test			X	X (if not done at visit 3)				

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	5-8
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	6
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2,23

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	2
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic,	6-7

		academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	NA
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	NA
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7-8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8-9
Methods: Assignment of interventions (for controlled trials)			NA
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a	8

		description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8-9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these	9

		interim results and make the final decision to terminate the trial	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	supplementary materials
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14
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Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
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Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
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trial care		and for compensation to those who suffer harm from trial participation	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
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Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	supplementary materials
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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Hyperkalemia prevalence, recurrence, and treatment in patients on haemodialysis in China: protocol for a prospective multicentre cohort study (PRECEDE-K)

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Hyperkalemia prevalence, recurrence, and treatment in patients on haemodialysis in China: protocol for a prospective multicentre cohort study (PRECEDE-K)

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ABSTRACT

Introduction: Hyperkalemia (HK) is a potentially life-threatening electrolyte imbalance associated with several adverse clinical outcomes and is common in patients with kidney failure. However, there is no evidence on the occurrence, recurrence, and treatment of HK in patients on hemodialysis (HD) in China.

Methods and analysis: The HK Prevalence, Recurrence, and Treatment in Haemodialysis Study (PRECEDE-K) is a prospective, multicenter, observational, cohort study being conducted across 15-18 sites in China. Approximately 600 patients with end-stage kidney disease on HD are anticipated to be enrolled and will be followed up for 24 weeks. Patients will be in the long interdialytic interval (LIDI) at enrollment and will receive follow-up care every 4 weeks in LIDI for pre-dialysis and post-dialysis (at enrollment only) serum potassium measurements. To obtain pre-dialysis serum potassium levels in the short interdialytic interval (SIDI), a follow-up visit will be performed in the SIDI during the first week. Information on concomitant medications, blood gas analysis, and biochemistry measurements will be obtained at enrollment and

at each follow-up visit. The primary endpoint will be the proportion of patients experiencing HK (defined as serum potassium level >5.0 mmol/L) at the study enrollment or during the 24-week follow-up. The key secondary endpoint will be the proportion of patients experiencing HK recurrence (defined as any HK event after the first HK event) within 1 to 6 months (if applicable) during the 24-week follow-up, including enrollment assessment.

Ethics and dissemination: This study has been approved by Shanghai Jiaotong University School of Medicine, Renji Hospital Ethics Committee (2020-040). Other participating sub-centers must also obtain ethics committee approval prior to the start the study. The Good Clinical Practice (GCP) regulations shall be strictly followed during the test implementation. Amendments to the protocol will be reviewed by the ethics committees. Written informed consent will be obtained from all participants before collection of any patient data and patient information. The findings of this study will be disseminated through peer-reviewed publications and conference presentations.

Study registration: ClinicalTrials.gov, NCT04799067.

Key words: dialysis, end-stage renal failure, epidemiology

Strengths and limitations of this study

- This will be the first prospective study on the prevalence, recurrence, and treatment pattern of hyperkalemia in patients on hemodialysis in China and will provide high-quality evidence and meaningful insights for guiding physicians in clinical practice.
- The study will provide data on the treatment patterns for different options for the management of hyperkalemia in hemodialysis patients, but will not focus on the efficacy, safety and tolerability of different treatments.
- The study will not focus on the prognosis or the impact on cardiovascular events of hyperkalemia.

Introduction

The prevalence of end-stage renal disease (ESRD) is on the rise globally. In 2010, 2.618 million patients with ESRD received renal replacement therapy (RRT) worldwide and its use is projected to be more than double by 2030, with the highest prevalence in Asia.[1] Hemodialysis (HD) is the dominant treatment modality for those who are under RRT in China. According to the Report of Chinese National Renal Data System (CNRDS) in 2018, there were >1.3 million patients with ESRD in China, among whom there were 580,000 patients who were on HD.

Hyperkalemia (HK), a potentially life-threatening electrolyte imbalance can be classified depending on the severity of serum potassium (sk) levels as mild (5.1-5.9 mmol/L), moderate (6.0-6.9 mmol/L) and severe (≥ 7 mmol/L).[2] Due to its detrimental effects on cardiac electrophysiology and neuromuscular function, HK has been proved to be associated with several adverse clinical outcomes, including significant arrythmia, hospitalization and associated length of stay, and all-cause mortality[[3–5]]. HK is common in patients with kidney failure due to diminished renal potassium excretion, with a prevalence of 30% to 50% in patients with ESRD under maintenance HD worldwide, and is recognized as a risk factor for sudden death and all-cause mortality in patients on HD[6,7]. Chinese patients with ESRD have different spectrum of chronic kidney disease (CKD)[8], and different dietary style and treatment patterns,[9] thus they may have distinct characteristics of HK occurrence and recurrence. Besides, abnormalities of potassium, rapid changes in potassium

concentrations during the HD session have been suggested as a potential cause of cardiac arrhythmia.[10–13] High dietary K^+ intake has been associated with increased 5-year mortality rates in patients on HD. Therefore, dietary K^+ intake should be restricted to 2000 mg/day and patients should be educated about dietary habits and dietary regimens should be personalized for individual patients. Moreover, HK can be managed by changes in dialysis prescriptions like potassium dialysate (K^+ D) concentration and number of HD sessions.[14] A higher incidence of predialysis HK after the long interdialytic interval (LIDI) was observed with K^+ D ≤2 mmol/L versus ≥3 mmol/L). Also, 3-times-weekly HD is associated with excess volume and metabolic fluctuations during the LIDI predisposing to cardiovascular morbidity and mortality.[14]

However, there is no evidence on the occurrence, recurrence, and the treatment of HK in patients undergoing HD in China. Meanwhile, there is no Chinese guidelines on HK management in patients undergoing HD. In the present study, we aimed to evaluate the prevalence and recurrence of HK in Chinese patients on HD and to understand the treatment pattern of HK in China.

Methods and analysis

Design

This is a prospective, observational, cohort study, which was registered with the ClinicalTrials.gov (NCT04799067) prior to initiation of patient enrollment.

Patients will be in long interdialytic interval (LIDI) at enrollment visit 1 (V1). Demographic characteristics, medical history, etiology of ESRD, concomitant

medications, dialysis vintage, concentration of potassium dialysate (0, 1, 2 ,3 mmol/L or other concentration) an electrocardiogram, a pre-dialysis K^+ measurement and a post-dialysis K^+ measurement, blood routine, blood gas analysis, and other blood biochemistry measurements will be obtained. Potassium measurements, including pre-dialysis potassium measurements at the LIDI once every month (V3-V8), pre-dialysis potassium at short interdialytic interval (SIDI) during the first week (V2) for patients in HD thrice a week specifically, will be performed. Information on concomitant medications, blood routine, blood gas analysis, and other blood biochemistry measurements will also be obtained. Besides that, evaluation of the different ions (K +, Na, Mg, Ca and P) on a monthly basis, during the follow-up time with the different potassium chelators in patients on HD will be conducted. In this study, control on dietary intake of potassium and dialysis prescription management will be carried out for the control of hyperkalemia in addition to the therapeutic.

LIDI is defined as the interval between dialysis ≥2 days, while SIDI is defined as the 1-day interval between dialysis. For patients receiving HD thrice weekly, there will be one LIDI and two SIDI every week. For patients receiving HD twice a week, there will be two LIDIs every week.

The illustration of the proposed study design is shown in Figure 1 (patient on HD thrice a week as an example). The detailed study plan of the PRECEDE-K study is shown in Table 1.

Table 1. The Study Plan of the PRECEDE-K Study

	Visit 1	Visit 2	Visit 3-8
	1d (LIDI)	3/5d [a](SIDI)	4-24 w[b] (LIDI)
ICF	X		
Screen inclusion and exclusion criteria	X		
Demographic characteristics	X		
Medical history	X		
Etiology of ESRD	X		
Vascular access	X		X
Height (cm)	X		
Pre-dialysis weight (kg)	X	X	X
Post-dialysis weight (kg)	X	X	X
Vital signs	X	X	X
Physical examination	X	X	X
Pre-dialysis serum K^+ [c] mEq/L	X	X	X
Post-dialysis serum K^+ [c] mEq/L	X		X*
Dialysis adequacy[d]	X		Evaluated at week 12
Dialysis frequency	X		X
Dialysis prescription	X		X
ECG[e]	X		X*
Echocardiography[f]	X*		X*
Urine 24-hour volume (litres)[g]			Evaluated at week 4 or week 8
Urine biochemistry measurements[g]			Evaluated at week 4 or week 8
Ultrafiltration rate	X		X
Blood routine	X		X
Biochemistry measurements	X		X
Blood gas analysis	X		X
Concomitant medication	X	X	X

Vital signs, physical examination, pre-dialysis K^+, pre-dialysis weight, blood routine, biochemistry measurements should be collected within 30 minutes before initiation of HD. Post-dialysis weight, post-dialysis K^+ and post-dialysis BUN should be collected within 30 minutes after HD procedure.

All blood samples will be measured at local laboratory.

d, day; ECG, electrocardiogram; ESRD, end-stage renal disease; ICF, intracellular fluid; LIDI, long interdialytic interval; SIDI, short interdialytic interval; w, week;

[a]For patients receiving HD thrice a week, there are 2 SIDI in an HD section, so visit 2 can be on day 3 or day 5. For patients receiving HD twice a week, visit 2 will be waived, as there is no SIDI for these patients.

[b]Time window is ±1week.

[c]Blood samples for the determination of pre-dialysis serum K^+ concentration and post-dialysis serum K^+ concentration will be drawn before and after the HD procedure according to the routine clinical practice.

[d]Dialysis adequacy will be evaluated by URR. . To calculate the URR, post-dialysis BUN will be tested on day 1 and week 12.

[e]ECG: evaluated within 1 day before or after the enrollment in principle; allow individual adjustments in each center. All ECGs during the follow-up should be recorded in eCRF. For patients who experience HK during the study period, it is recommended to conduct at least one more pre-dialysis ECG at LIDI.

[f]Echocardiography: evaluated echocardiography data if it is conducted within 2 weeks before or after visits in principle; allow individual adjustments in each center.

[g]Urine will be collected for a period of 24 hours at either week 4 or week 8. The volume and biochemistry measurements of the 24-hour urine sample will be measured.

Study sites and period

This study will utilize primary data collected by investigators from approximately 15-18 sites in China. Patients with ESRD on HD treatment will be enrolled and will be followed up for 24 weeks.

Population

This study will include approximately 600 patients with ESRD (aged ≥18 years) receiving HD treatment twice a week or thrice a week. Written informed consent will be obtained from all the participants (Supplementary file). Patients will be eligible to be included in the study only if all of the following criteria are applicable: (1) patients are aged ≥18 years at the time of signing the informed consent; (2) patients with ESRD and on HD; (3) the HD treatment frequency is ≥2 sessions per week; (4) capable of giving signed informed consent.

Patients will be excluded from the study if any of the following criteria are applicable: (1) acute kidney injury; (2) expected to receive renal transplantation within 6 months; (3) intracranial hemorrhage or elevated intracranial pressure within 1 month before

enrollment; (4) a traumatic experience that cannot be corrected by drugs within 1 month before enrollment; (5) failure to establish vascular access; (6)has been receiving peritoneal dialysis; (7) not suitable for this study as judged by the investigators

Procedures for Withdrawal/Discontinuation

Eligible patients will be followed for up to 24 weeks, or up till occurrence of any of following events, whichever occurred earlier.

1. Death
2. End of study period
3. Loss to follow-up: defined as transfer to HD centre(s) not in this study, or refused to continue follow-up, or cannot be contacted by phone calls for three times
4. Change modality of RRT (peritoneal dialysis or renal transplantation)
5. Withdrawal of ICF
6. Investigators consider it necessary for the subjects to terminate the study

Primary outcome

The primary outcome will be proportion of patients experiencing HK (defined as serum potassium levels >5.0 mmol/L) at the study enrollment or during a 24-week follow-up.

Secondary outcomes

- The proportion of patients experiencing HK recurrence (defined as any HK event after the first HK event) within 1, 2, 3, 4, 5, or 6 months (if applicable) during a 24-week follow-up including the enrollment assessment. An HK event is defined as any serum K^+ concentration >5.0 mmol/L within an interdialytic interval, which is usually 2 to 3 days.
- The proportion of patients with 2, 3, 4, 5, and ≥6 events of HK during a 24-week follow-up including the enrollment assessment.

- Intradialytic potassium shift (defined as the difference between pre- and post-dialysis K^+ concentration) at LIDI during the first week after patient enrollment
- Serum K^+ concentration at LIDI and SIDI in patients receiving HD thrice a week during the first week after patient enrollment.
- The proportion of patients with HK treated with any potassium binders including sodium polystyrene sulfonate (SPS), calcium polystyrene sulfonate (CPS), or sodium zirconium cyclosilicate (SZC), and specific proportion of each potassium binder, respectively, during the 24-week follow-up period.
- The proportion of HK events treated with any potassium binders including SPS, CPS, or SZC among total number of HK events during the 24-week follow-up period.
- Mean daily dose of SPS, CPS, or SZC in patients treated with any potassium binder.
- Duration of the treatment of SPS, CPS, or SZC in patients treated with any potassium binders.

Exploratory endpoints

- Risk factors for experiencing any HK (defined as serum potassium level >5.0 mmol/L) at the study enrollment or during a 24-week follow-up.
- Risk factors for experiencing HK recurrence during a 24-week follow-up.
- The efficacy, safety and tolerability of the options for the management of hyperkalemia in hemodialysis (HD) patients.

Statistical analysis principles

Statistical methods will be primarily descriptive in nature. For categorical data, the frequency and percentage of patients in each category will be presented. Percentages will be based on non-missing data unless otherwise specified. For continuous data, descriptive statistics will be presented as the number of patients (n), mean, standard deviation (SD), median, minimum and maximum. All successfully enrolled subjects fulfilling inclusion/exclusion criteria will be included in the Full Analysis Set (FAS), which will be the primary analysis set for all primary and secondary analyses unless specified otherwise.

Primary analysis

The proportion of patents experiencing any HK at the study enrollment or during a 24-week follow-up will be presented by the percentage as well as its 95% confidence interval. HK is defined as K^+ >5.0 mmol/L while the same summary will be generated using a higher threshold of HK as K^+ >5.5 mmol/L as well, as sensitivity analysis. The proportion of patients experiencing serum K^+ concentration >6.0 mmol/L, 6.5 mmol/L, 7.0 mmol/L, and 7.5 mmol/L will be reported as well.

Secondary analysis

1. The proportion of HK recurrence within 1, 2, 3, 4, 5, or 6 month(s) after the first HK and the proportions of patients with 2, 3, 4, 5, and ≥6 times of HK events during the 24-week follow-up will be presented using the percentage and its 95% confidence interval.

The HK recurrence is defined as any consecutive HK events. An HK event is defined as any serum K^+ concentration >5.0 mmol/L within an interdialytic interval, which is usually 2 to 3 days. A higher threshold of HK event as serum K^+ concentration >5.5 mmol/L will be utilized to generate similar summaries, as sensitivity analyses.

2. Intradialytic potassium shift is evaluated by the mean difference between pre- and post-dialysis serum K^+ concentration during the first week after patient enrollment. If there are more than one serum K^+ concentrations before or after HD, intradialytic potassium shift will be the difference between the last serum K^+ concentration measurement before HD and the first serum K^+ measurement after HD. Summary statistics will be provided using mean, median, SD, minimum, and maximum. The number of subjects and the missing number of subjects will also be presented.

3. Serum K^+ concentration at LIDI and SIDI as well as the difference between LIDI and SIDI during the first week after patient enrollment will summarized with the same method as described above. This analysis will only be applicable on patients receiving HD thrice a week. LIDI is defined as the interval between dialysis (≥2 days), whereas SIDI is defined as the 1-day interval between dialysis.

4. Treatment pattern for HK with potassium binders will be assessed by: the proportion of HK patients treated with any potassium binders including SPS or CPS or SZC during the 24-week follow-up period. The proportion of patients with HK treated with specific potassium binder including SPS, CPS, and SZC, respectively, during the 24-week follow-up period; the proportion of HK events treated with any potassium binders

including SPS, CPS, or SZC among total number of HK events during the 24-week follow-up period; the mean daily dose of SPS, CPS, or SZC in patients treated with any potassium binder; the duration of the treatment of SPS, CPS, or SZC in patients treated with any potassium binder, above the categorical and continuous variables will be analyzed based on previously mentioned descriptive methods, as associated summary statistics, will be presented. Where for proportion, the denominator will always be the number of subjects in FAS.

Exploratory analysis

Univariate and multivariate logistic regression will be used to explore the association of risk factors with any HK occurrence and recurrence. HK occurrence is defined similar to that mentioned in the primary analysis, where patients experience any HK (defined as serum potassium >5.0 mmol/L) at the study enrollment or during a 24-week follow-up. The HK recurrence is defined similar to that mentioned in the secondary analysis, where patients experienced any HK event after the first HK event will be counted as with recurrence. An HK event is defined as any serum K^+ concentration >5.0 mmol/L within an interdialytic interval, which is usually 2 to 3 days. Risk factors including dialysis frequency, dialysate potassium, dialysis vintage, treatment of HK, medical history of special interest, including history of atherosclerotic heart disease, congestive heart failure, diabetes, hypertension, uncontrolled asthma on bronchodilators, dialysis adequacy (URR), urine volume, and so on. Odds ratio and 95% confidence interval estimation of each risk factor (both un-adjusted and adjusted) will be presented with 2-sided *P*-value provided. An exploratory sub-group analysis will be

set to evaluate the efficacy, safety and tolerability of the options for the management of hyperkalemia in hemodialysis (HD) patients.

Sample size and power calculations

The primary endpoint will be the proportion of patients experiencing HK anytime at enrollment and during a 24-week follow-up, the previously reported proportion of patients experiencing HK is 73.8% during a 2-year follow-up[9] and 58% during a 4-month follow-up.[11] In this study, an assumption is made that the proportion of patients experiencing HK will be between 58% and 73.8% during a 24-week follow-up. Precision estimates for primary endpoint under different sample sizes are presented in table 2. We assumed that 600 patients will provide a precision (half width of 95% confidence interval) estimate of 3.5% to 3.9%.

Table 2. Precision estimates for primary endpoint under different sample sizes

HK Proportion	Sample Size	Precision	95% Confidence Interval Estimate
58.0%	600	3.90%	[54.1%, 61.9%]
73.8%	600	3.50%	[70.3%, 77.3%]

HK, hyperkalemia

Data statement

All Data will be collected and entered into the electronic case report form (eCRF). The investigator will be responsible for ensuring that the required data is collected and entered into the eCRF.

Quality Control

The activities for quality control could include but are not limited to:

Contacts with the sites to

- Provide information and support to the investigator(s)
- Confirm that the research team is complying with the protocol and that data are being accurately recorded in the eCRFs
- Ensure that the subject ICFs are signed and stored at the investigator's site
- Ensure that the eCRFs are completed properly and with adequate quality.

Monitoring activities for:

- Checking of ICFs
- Checking that subjects exist in medical records

The extent and nature of monitoring will be decided during the study planning based on design, complexity, number of subjects, number of sites, etc.

Different signals (eg, high rejection rate in a site) should be used as potential identification of low protocol compliance by investigators.

If these or any other signal occurs or if the investigator is suspicious of a potential non-optimal level of protocol compliance by the site investigator, specific measures should be adopted to evaluate the situation, identify the issue and implement specific action plans to correct the situation.

Training of Study Site Personnel

The Principal Investigator will ensure that appropriate training relevant to the observational study is given to investigational staff.

Patient and Public Involvement

No patient involved.

Ethics and dissemination

This study has been approved by Shanghai Jiaotong University School of Medicine, Renji Hospital Ethics Committee (2020-040). Other participating sub-centers must also obtain ethics committee approval documents prior to the start of the study. The Good Clinical Practice (GCP) regulations shall be strictly followed during the test implementation. Amendments to the protocol will be reviewed by the ethics committees.

Written informed consent will be obtained from all participants before collection of any patient data or patient information. The findings of this study will be disseminated through peer-reviewed publications and conference presentations.

Discussion

HK is common in patients with kidney failure due to diminished renal potassium excretion despite the widespread and dynamic prescription of low-K^+ dialysis baths and K^+ binders. According to a prospective multicenter study in France, the percentage of patients with long-term HD experiencing HK at any time was 73.8% (K^+ >5.1 mmol/L), 57.9% (K^+ >5.5 mmol/L), and 34.5% (K^+ >6 mmol/L).[15] Another large retrospective study analyzed data derived from the United States Renal Data System (USRDS), reported that HK prevalence was consistently estimated at 16.3 to 16.8 events per 100 patient-months.[16]

Recently, an epidemiological study reported that the prevalence of HK in Chinese outpatients is 3.86%, and the prevalence of hyperkalemia in patients with CKD increased to 22.89%.[17] However, there is no high-quality evidence on the epidemiology of HK and no Chinese guidelines on the management of HK in Chinese patients on HD. The PRECEDE-K study will evaluate the prevalence of HK in Chinese patients on HD.

Previously, acute HK was considered as a fatal complication, however, with the deepened understanding of HK, emphasis have changed from acute HK to chronic HK in the recent years. Acute HK management involves cardiac monitoring, acute medical interventions, or possibly dialysis. However, chronic HK requires ongoing management

to correct the underlying disturbances in potassium balance including nonpharmacological and pharmacological interventions.[18] A higher rate of HK recurrence was observed 1, 2, and 3 months after an HK occurrence (e.g., 35.6% of HK cases with K^+ >6 mmol/L within 3 months after an initial HK of the same magnitude) in hepatic hemosiderosis in maintenance hemodialysis (MHD) patients despite widespread prescription of low-K^+ dialysis baths and K^+ binders).[15] Therefore, the proportion of patients experiencing HK recurrence is an important secondary outcome in this current study.

Compared with pre-dialysis K^+, post-dialysis K^+ is rarely investigated, and so its acceptable range remains unknown. Based on the difference between dialysate and serum potassium levels, serum potassium levels drop significantly after HD, and 45% of patients present with post-dialysis hypokalemia of <3.5 mmo/L in previous study.[19–21] Based on a cohort study of 3967 participants on MHD from the Dialysis Outcomes and Practice Patterns Study (DOPPS) in Japan (2009-2012 and 2012-2015) compared with post-dialysis potassium levels 3.0 to <3.5 mEq/L, the hazard ratios of post-dialysis hypokalemia (<3.0 mEq/L) were 1.84 (1.44-2.34) in the unadjusted model, 1.44 (1.14-1.82) in the model without adjusting for pre-dialysis serum potassium levels, and 1.10 (0.84-1.44) in the model adjusted for pre-dialysis serum potassium levels. This research suggested that post-dialysis hypokalemia was associated with mortality, but this association was not independent of pre-dialysis potassium.[22] Therefore, we regarded intradialytic potassium shift (defined as the difference between pre- and post-dialysis K^+) as a secondary outcome in our research.

A retrospective study reported that the prevalence of HK on the day after the LIDI was 2.0 to 2.4 times as high as on the day after the SIDI in patients with MHD.[16] The LIDI was reported as a time of heightened risk among patients receiving HD.[23] Serum K^+ levels at LIDI and SIDI in patients receiving HD thrice a week during the first week after patient enrollment was another secondary outcome.

The development of HK is usually the result of a combination of factors superimposed on comorbidities (eg, diabetes mellitus, advanced stages of heart failure), use of potassium-based salt substitutes, and use of medications interfering with potassium homeostasis-like angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), aldosterone receptor antagonists, β-blockers, and others.[24] Considering the potential risk factor of HK, we will record all the comorbidities and drugs in this study for further exploration.

Compared with the reference group of serum potassium level of 4.0 to 5.0 mEq/L, higher serum potassium level (5.6-6.0 mEq/L) was associated with mortality in adjusted analysis (HR: 1.13, CI:1.06-1.20), and higher serum potassium levels (>6.0mEq/L) was associated with arrhythmia composite (includes sudden death or arrhythmia-related hospitalizations) in adjusted analysis (HR: 1.21, 1.05-1.38).[25] Continuous rhythm monitoring was performed using the remote-monitoring capability of the implantable loop recorder device in patients undergoing HD at 8 centers.[26] In multivariate survival frailty analyses, a higher risk for conduction disorder was associated with plasma potassium levels >5.0 mmol/L. Further understanding and management of HK will benefit the survival in MHD patients.

However, while our study will provide data on the treatment patterns for different options for the management of HK in HD patients, it will not focus on the efficacy, safety and tolerability of different treatments. Additionally, the study will not focus on the prognosis or the impact on cardiovascular events of HK.

Conflicts of interests

The authors declare no competing interests.

Funding

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Author statement

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Sub-PI and writing, Haijiao Jin;

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Conception and design，Qing Zhao.

Figure 1. The study design of the PRECEDE-K study

*For patients receiving HD thrice a week, V2 could be at D3 or D5 for collecting pre-dialytic serum potassium at SIDI. For patients receiving HD twice a week, visit 2 will be waived as there is no SIDI for these patients; thus, there are 7 visits in total.
**Time window is ± 1 week.

d, day; ESRD, end-stage renal disease; LIDI, long interdialytic interval; SIDI, short interdialytic interval; V, visit; w, week

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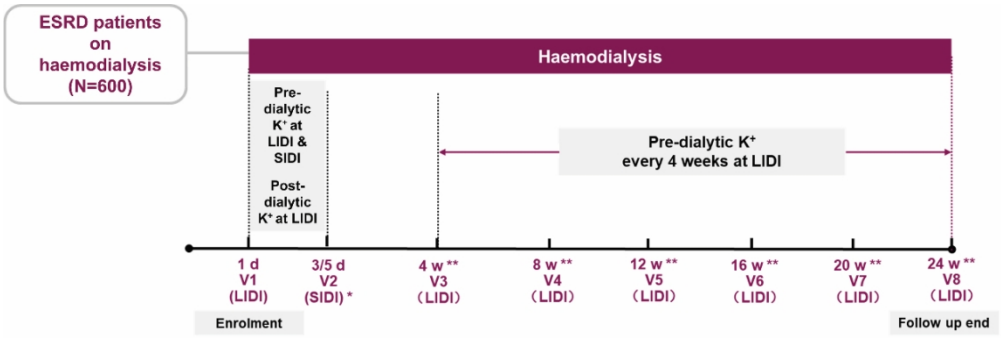
Word count 4868.



The study design of the PRECEDE-K study

374x125mm (86 x 86 DPI)

STUDY INFORMATION AND INFORMED CONSENT FORM

There are [4] parts to this document:

Part I: the "**Study Information**" essential to your decision to take part in the clinical study.

Part II: the "**Future Research Information**" which explains the possibility to contribute to future research.

Part III: your "**Consent Form**" which summarise what you may agree to.

Part IV: supplementary information in the "***Additional information for patients***" Section.

PART I: STUDY INFORMATION

[Study number D9480R00033]

Title of study: Hyperkalaemia Prevalence, Recurrence and Treatment in Haemodialysis: A prospective multi-centre cohort study

Dear Madam/Sir,

You are invited to take part in this study because you are diagnosed with end stage renal disease (ESRD) and is on haemodialysis (HD). Participation requires your written consent. Before you decide whether you want to participate in this study, you will be given an explanation about what the study involves.

The overall description of this study has been reviewed by an independent Ethics Committee to ensure that the rights, safety and well-being of study patients are protected.

Your condition may not improve if you join the study. But, the information we get from this study might help other patients with the same condition in the future.

1 What is this study about?

We are doing this study to learn more about occurrence and recurrence of hyperkalaemia（HK） in Chinese HD patients and to understand the treatment pattern of HK in China and also to better understand the risk factors associated with HK.

About 600 people from approximate 15 hospitals will take part in this study.

2 Do I have to take part?

You have a choice whether or not you would like to participate.

Please take as much time as you need to make a decision about whether or not you would like to participate in this study. It may be helpful to talk with your friends and family as you make this decision.

If you join the study, you can leave at any time (see “section 10” for more details). Leaving will not affect your care. If you choose to leave the study, please let your study doctor know as soon as possible.

If you don’t join the study, you will continue to receive care for your disease. Your study doctor or treating physician will talk to you about other possible treatments, their risks and benefits.

3 What will happen if I join the study?

Because this is an observational study, no medications or other treatments are provided to you by the Sponsor as part of this study.

You will continue to come for your routine doctor’s appointments and to take your regular medication as prescribed by your doctor.

You will be in the study for about 6 months.

During the visits, information will be collected for the study and this might add some extra time to your routine visit of approximately 10 minutes.

If you cannot come to a visit, you must tell your study doctor.

Please note that the study, and your participation in the study, may be stopped earlier than expected, for example for scientific or safety reasons (see “section 6” for more details).

4 What are the required tests and procedures?

To conduct the study, some tests and procedures will have to be performed on you.

In addition to the standard of care examinations for the disease the following tests and procedures will be included:

- **Enrolment(Day 1, 1 visit)**: You will be in Long interdialytic interval (LIDI) at enrolment.

  ✓ Demographic characteristics

  - Your general information such as age, gender and race will be collected.

  ✓ Medical history, Etiology of ESRD

  - Your study doctor will collect information about your medical history (history of previous disease and surgery history) and the cause of ESRD.

  ✓ Clinical evaluations and laboratory tests

  - Clinical evaluations, which include vascular access, physical examination, height, pre-dialysis and post-dialysis weight, electrocardiography (ECG), echocardiography(not mandatory), blood pressure, pulse, heart rate will be performed.
  - You blood will also be tested for pre-dialysis and post-dialysis serum K+, pre-dialysis BUN and post-dialysis BUN, Blood routine, Biochemistry measurements, Blood gas analysis.
  - Dialysis prescription and frequency will be collected. Dialysis adequacy will be evaluated.

  ✓ Concomitant medication

  - Any medication used by you while participating in this study will be collected for dosage, duration and mode of administration.

- **Follow-up(24 weeks, 7 or 8 visits)**: You will be in short interdialytic interval (SIDI) at visit 2 (if applicable) and in LIDI at visit 3-8.

  Visit 2(Only applicable for HD received thrice a week)

  ✓ Clinical evaluations and laboratory tests

  - Clinical evaluations, which include physical examination, pre-dialysis and post-dialysis weight, blood pressure, pulse, heart rate will be performed.
  - You blood will also be tested for pre-dialysis serum K+.

✓ Concomitant medication

- Any medication used by you while participating in this study will be collected for dosage, duration and mode of administration.

Visit 3-8

✓ Clinical evaluations and laboratory tests

- Clinical evaluations, which include vascular access, physical examination, pre-dialysis and post-dialysis weight, electrocardiography (ECG, not mandatory), echocardiography(not mandatory), blood pressure, pulse, heart rate will be performed when you visit the study site according to the study schedule.
- You blood will also be tested for pre-dialysis and post-dialysis serum K+(not mandatory), pre-dialysis BUN and post-dialysis BUN, Blood routine, Biochemistry measurements, Blood gas analysis when you visit the study site according to the study schedule.
- Dialysis prescription and frequency will be collected, and dialysis adequacy(evaluated at V5) will be evaluated at each visit.
- Urine 24- hour volume and biochemistry measurements will be performed at V3 or V4.

✓ Concomitant medication

- Any medication used by you while participating in this study will be collected for dosage, duration and mode of administration at each visit.

The complete list of tests and procedures, including their detailed schedule is available in “part 4: Additional Information for Patients”.

5 What are the risks and possible benefits of joining the study?

There is no immediate clinical benefit for you, however the information we get from this study may help us to describe how HD patients with HK are managed in real-life practice, and to increase our knowledge about the disease and its symptoms. This will hopefully help us to better treat HD patients with HK in the future.

Since the study is observational, it will not change how your disease is managed by your doctor. There are no physical risks of taking part in this study.

6 What happens if something changes while I am in the study, e.g., if new information is found?

Changes may happen in the study that could make you change your mind about continuing to take part. If something changes, we will tell you as soon as possible.

You can choose to leave the study at any time. For more details see section 10 below.

The study doctor can also choose to take you out of the study if they believe that it is best for you.

Your participation in the study also stops when the Sponsor, health authorities, the ethics or regulatory agencies decide that the study must be stopped.

7 What happens if I am harmed or injured during the study?

If you become ill or are injured while you are in this study, you must tell your study doctor straight away.

Injuries that have been caused by the study tests or procedures are called 'research injuries'. Injuries caused by your usual medical care or your disease, are not research injuries.

The Sponsor has an insurance to cover the costs of research injuries as long as you have followed your study doctor´s instructions. Sponsor will pay the costs of medical treatment for research injuries, provided that the costs are reasonable, and you did not cause the injury yourself.

8 What will happen to my data gathered in the study?

a. Which data are collected?

In order to conduct the study, the Study site will have to collect and register information about your identity (such as your name, address, telephone number) as well as data that is necessary to assess your health conditions, your medical condition and medical history (this may include information from your physicians/ available in your medical records), your demographics (age, gender, *ethnic*).

b. What are my data needed for?

Your data are needed to better understand the studied disease and associated health problems and publish research results in scientific journals or use them for educational purposes.

c. Who can access my data?

Only at the study site, your name and contact details will be accessible to the study doctor and the study team to conduct the study. Non-medical personnel acting on behalf of the sponsor and being bound by a duty of confidentiality as well as Health authorities and Ethics Committees may also be given access to this data only to verify that the study is carried out in compliance with legal and quality requirements.

The study site will share your data with the sponsor but only after they have been coded (which means that your name, contact details have been replaced by a code). The sponsor may share your coded data with its Research partners and Service providers for the purposes of a drug development programme.

In order to ensure proper conduct and accurate results of the study the sponsor will share your coded data with authorities and possibly with Ethics Committees. They may also be shared with scientific journals, so the study results can be reviewed by independent scientists and to ensure the accuracy of results.

In **none** of these cases your identity will be revealed.

Some of the above-mentioned persons may be located outside your country. If this other country does not have equivalent personal data protection standards than your country, appropriate Safeguards (such as contracts and technical Security measures) will be adopted to protect and maintain the confidentiality of your data.

d. How long will my coded data be kept?

The study site and the sponsor are obliged to keep all study data for a number of years to comply with study site's and Sponsor's legal obligations. You can find out more about how the sponsor keeps personal information at www.astrazenecapersonaldataretention.com. Your coded data will then be deleted or anonymised.

e. What are my rights under data protection law?

Subject to local laws, *y*ou have the right to review which of your data are collected and being used;

To ensure the scientific integrity of the study, you will not be able to review some of the data or receive a copy of it until the study ends.

f. What does anonymised data mean?

Health authorities as well as pharmaceutical companies believe that access to clinical studies data advances clinical science and medical knowledge and is in the best interest of patients and public health, provided that patient privacy is protected. Therefore, the

sponsor may generate and share internally or with other researchers an anonymised set of your data collected in the study (e.g., on www.clinicalstudydatarequest.com). This means your coded data will be stripped of your Patient code as well as of any other information that could reasonably be used to identify you such as your date of birth.

9 What are the costs of taking part?

Participating in this study will not cost you anything more than the costs related to your routine appointments with your doctor. You will not be paid for being in this study.

You may be reimbursed for reasonable expenses incurred due to your participation in the study (for example: travel). If so, you will be paid RMB 150 per visit per protocol.

10 What will happen if I want to quit the study?

Your participation in the study is voluntary which means you can stop your participation at any time. If you want to stop your participation, you should tell the study doctor.

If you stop participating in the study, the study doctor will stop the collection of your data but your previously collected data will be kept and used to guarantee the validity of the study and comply with regulatory requirements, as allowed by law. The study doctor will then invite you to have an end of study examination to check your wellbeing. If you don't show up at a planned visit, the study doctor will try to reach you. If the study doctor cannot reach you, public sources will be consulted to verify your wellbeing. This is important for study results. It is not mandatory but would be helpful for the study if you explain to your study doctor why you wish to stop your participation, in particular if you have experienced discomforts.

If you would like your data not to be used after you quit the study, you must inform the study doctor. In such case, your coded data previously collected will be kept as required by clinical regulations.

11 Who can answer any questions I may have?

Shanghai Jiaotong University School of Medicine, Renji Hospital Ethics Committee has reviewed the plans for this study to make sure that people who take part in this study are protected from harm.

If you have any questions about your rights during your taking part in this study, you can contact:

< Qi Lu, 021-58752345 , Dongfang Road 1630, Shanghai, China >

If you have any questions about the study, please contact:

Study doctor Haijiao Jin	Study Coordinator (e.g. nurse appointed to the study) <*insert details*>
Phone No. 13917735313	Phone No. <*insert details*>
Address Dongfang Road 1630, Shanghai, China	Address <*insert details*>

12 How to find out more after the study?

Information about this study will be posted on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov. These websites do not contain any information about you. You can visit this website for more information. You may also get other information about your participation in the study from Sponsor via your study doctor.

PART 2: FUTURE RESEARCH INFORMATION

In addition to participating in the study, we would like to know if you would be willing that your coded data are used in future research projects with appropriate ethical approval.

You are free to consent to the use of your coded data for future research. If you decide not to do so, you may still take part in the clinical study.

1 What is future research?

Future research is important to advance science and public health. At present, however, it is not possible to foresee all details of future scientific research projects. These future scientific research projects are beyond the scope of the study and use of data as outlined in part 1 and may occur whilst the study is ongoing or after the study has finished.

Your coded data may only be used for scientific health-related research to find new ways to detect, treat, prevent or cure health problems.

They may also be used jointly with information from other sources outside typical clinical research settings, e.g. from public research databases. However, they will not be combined with other information in a way that could identify you. Your coded data and may also be anonymized for some of the future scientific research.

2 May my coded data be shared?

The sponsor may share your coded data with research partners. This may include researchers from research hospitals, and companies.

Some of the above-mentioned recipients may be located outside your country. The data protection laws which apply in those countries may not be as stringent as the laws in your country. Nevertheless, appropriate safeguards and security measures will be taken in order to protect and maintain the confidentiality of coded data.

3 How will my privacy be protected?

Your coded data will be subject to appropriate safeguards, and will only be used for the purpose of scientific health related research. They will not be used to contact you or to affect your care or any other decision affecting your life such as insurance rates or employment opportunities.

4 What if I want to withdraw from future research?

Your participation in future research is voluntary. You are entitled to withdraw your consent for future research at any time, without giving a reason and without a negative effect on your standard of medical care. If you wish to withdraw, please inform your study doctor.

You may still continue to participate in the research study even if you choose to withdraw from future research.

If you withdraw from future research, your coded data will not be used for future research. Your coded data (either copied from the research study database or newly generated) will also be destroyed unless this information is already included in analyses or used in scientific publications or if the coded data been anonymized and therefore we can't identify your data.

5 Results from Future Research?

We may have to study coded data from many people over many years before we can know if the results of future research are meaningful.

Therefore, you should not expect to receive individual results from future research projects. We will not give any such data to your doctor and we will not put them in your medical record as they are not individual valid results.

You are free to consent to the use of your coded data for FUTURE RESEARCH. If you disagree, you can indicate this in the CONSENT FORM.

PART III: CONSENT FORM

Study Code:	D9480R00033	Site No:	
Sponsor:	AstraZeneca China	Investigator:	
Study Title:	Hyperkalaemia Prevalence, Recurrence and Treatment in Haemodialysis: A prospective multi-centre cohort study		

I confirm that:

- The study doctor or study personnel delegated by the study doctor has explained the study to me comprehensively.
- I have had the opportunity to discuss the study with the study doctor and all my questions were answered.
- I have had an adequate amount of time to consider the study.
- I have read and understood all the above information related to the study.
- I understand that I will receive a copy of this document once I have signed it.
- I understand that my decision to take part in the study is entirely voluntary. If I decide not to participate in the study or to stop my participation during the study, this will not affect my standard medical care.
- I have truthfully answered all questions about my medical history and will follow all rules listed in the document.

I consent to take part in the research study and study procedures described herein. I understand that my participation also entails:

- My name and contact details being collected during the study as described to me, and accessed and reviewed by listed authorised people;
- My coded data being used by the sponsor or by people or companies acting on its behalf or working with the sponsor;
- My coded data being used by persons or organisations located in countries that do not have data protection rules equivalent to those of my country. I understand that the sponsor monitors these uses and takes all possible measures to protect my privacy;

SIGNATURE CONSENT FORM

Signature of participant	Date of Signature
Printed name of participant	
Signature of person conducting the informed consent discussion	Date of Signature
Printed name of person conducting the informed consent discussion	

Please complete the following if legally accepted representative or impartial witness is applicable.

Signature of legally accepted representative	Date of Signature
Printed name of legally accepted representative	
Relationship of legally accepted representative to participant	
Signature of impartial witness	Date of Signature
Printed name of impartial witness	

When signed and dated, we will give you a copy of this form.

PART IV: ADDITIONAL INFORMATION FOR PATIENTS

1 Sponsor details:

Sponsor details	Sponsor: AstraZeneca Investment (China) Co., Ltd, No.199 Liangjing Road Shanghai 201203, China The sponsor has the overall responsibility for the research study.

2 Detailed list of visits and Test/Procedures

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	day 1	day 3 or 5	week 4	week 8	week 12	week 16	week 20	week 24
Pre-dialysis serum K^+	X	X	X	X	X	X	X	X
Post-dialysis serum K^+	X							
Pre-dialysis BUN & Post-dialysis BUN	X				X			
Blood Sample Collectionroutine	X		X	X	X	X	X	X
Blood Biochemistry measurements	X		X	X	X	X	X	X
Blood gas analysis	X		X	X	X	X	X	X
Urine 24- hour volume & Urine samplebiochemistry test			X	X (if not done at visit 3)				

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	5-8
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	6
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2,23

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	2
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic,	6-7

		academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	NA
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	NA
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7-8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8-9
Methods: Assignment of interventions (for controlled trials)			NA
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a	8

		description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8-9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these	9

		interim results and make the final decision to terminate the trial	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	supplementary materials
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	14
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care,	NA

trial care		and for compensation to those who suffer harm from trial participation	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	23
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	supplementary materials
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA