Principal Investigator: David Goldfarb, MD
Study Number: 17-00051
NCT Number: NCT03183778

1) **Protocol Title**

Use of patiromer to transition chronic kidney disease patients with hyperkalemia to a plant-rich diet

2) **Objectives**

The purpose of this proof-of-concept controlled-feeding study is to determine whether patiromer (Veltassa®, Relypsa, Inc., Redwood City, CA) can be used to maintain normal serum potassium concentrations in chronic kidney disease (CKD) patients who are transitioned to a plant-rich diet. We hypothesize that patriomer can be titrated to maintain serum potassium concentrations in the normal range, allowing CKD patients to consume a plant-rich diet without developing hyperkalemia. If successful, we plan to conduct a randomized clinical trial to determine the quality of life and health outcomes of CKD patients with hyperkalemia undergoing an intensive behavioral intervention to promote a low-potassium diet, or a plant-rich diet plus patiromer.

3) **Background**

An estimated 22.5% of adults 60 years and older in the U.S. have stages 3-5 CKD[1]. Individuals with stages 3-5 CKD are at increased risk of high blood potassium concentrations (hyperkalemia), which in severe cases can disrupt the normal contractility of the heart[2]. Several factors are thought to contribute to hyperkalemia in CKD patients, in particular diabetes, dietary potassium intake, and medications that inhibit the renin-angiotensin-aldosterone system (RAAS inhibitors, which include angiotensin converting enzyme inhibitors and angiotensin 2 receptor blockers; ACEi and ARBs)[3,4]. Given the potential health consequences of hyperkalemia, stages 3-5 CKD patients, even those without hyperkalemia, are often directed to follow a low-potassium diet[4].

Unfortunately, following a low-potassium diet involves limiting or avoiding many plant-based sources of potassium, including nuts, seeds, legumes, and high-potassium fruits and vegetables. With accompanying dietary restriction requirements for sodium, phosphate and protein, the diet can be burdensome and unpalatable for the patients, and can make it difficult to obtain essential nutrients[4]. In addition to providing potassium, high-potassium plant foods are important sources of dietary fiber, organic anions (potential base), antioxidants and other phytochemicals (e.g., phytosterols), and therefore, a low-potassium diet may contribute to hypertension (low potassium), constipation and diarrhea (low fiber), dysglycemia and dyslipidemia (low fiber and other phytochemicals), metabolic acidosis (low organic anions), oxidative stress and inflammation (low antioxidants and other phytochemicals)[4].

Patiromer is approved by the U.S. Food and Drug Administration (FDA) for the treatment of hyperkalemia, and has been demonstrated to be effective in treating hyperkalemia in CKD patients[5]. However, the potential of this new therapy for allowing CKD patients to liberalize their diets, and the potential health benefits of following a plant-rich diet in advanced CKD are yet unexplored.

4) **Inclusion and Exclusion Criteria**

The focus of the study is to: a) evaluate the efficacy of patiromer for managing serum potassium concentrations in CKD patients as they are transitioned to a plant-rich diet that includes high-potassium fruits and vegetables, and b) evaluate the impact of a plant-rich diet on health outcomes in CKD patients. We will recruit 10 CKD patients with persistently elevated serum potassium concentrations in New York City.

i. Inclusion criteria. In order to be eligible for the study, the individual must meet the following criteria:

a) 19-80 years of age

b) Stages 3-4 CKD (estimated glomerular filtration rate (eGFR) of 15-59 mL/min/1.73m^2, not

treated with dialysis)
c) No prior treatment with patiromer
d) Mild hyperkalemia (potassium 5.1 to <6.5 mEq/L) on one of the last two blood tests
e) No prior episodes of moderate-severe hyperkalemia (potassium ≥6.5 mEq/L) in the past 6 months
f) Deemed appropriate for the intervention by the patient's nephrologist, considering the patient's prognosis, cognition and pending treatments (e.g., dialysis)

ii. Exclusion criteria. We will exclude from participation patients with the following characteristics:
a) Change in medications that alter potassium homeostasis (e.g., RAAS inhibitors, diuretics, β-blockers) in the last month
b) Diagnosed with bowel diseases or syndromes (e.g., bowel obstruction, major GI surgery, short-bowel syndrome, irritable bowel syndrome, inflammatory bowel disease, chronic diarrhea)
c) Dietary restrictions (e.g., allergies) or otherwise unable/unwilling to adhere to study diets (excludes dietary restrictions on high-potassium foods)
d) Pregnant (females) or planning to become pregnant (males and females) during the study

If at any point during the study (including baseline) a participant has moderate-severe hyperkalemia (potassium ≥6.5mEq/L), or if a participant becomes pregnant during the study, they will be withdrawn from the study.

Inclusion of women and minorities

Given the pilot nature of the intervention and small sample size (n=10), the study population will not be representative of the CKD population, and will have insufficient power to detect differences in intervention effects by sex and race/ethnicity. To our knowledge, plant-rich diets, such as those being investigated in this study, have similar health effects by sex and race/ethnicity. No individual will be excluded from the study on the basis of sex or race/ethnicity alone, and we will attempt to obtain a sample that reflects the demographics of our source population.

5) **Study-Wide Number of Subjects**

We will recruit a total of 10 individuals to the study. We have secured the support of the New York Harbor VA Healthcare System, which served approximately 250 non-dialysis CKD patients in the New York City area, as well as the Division of Nephrology at NYU Langone Health. It is estimated that approximately 10% of these patients have hyperkalemia. Thus, we have no concerns about our ability to access and recruit the required number of participants for this study. The estimate demographic breakdown of patients at the renal clinic are 95% male with 40% white, 25% black, 20% Hispanic, 10% Asian, and 5% other racial/ethnic background. The planned enrollment is outlined in Table 1.

Table 1. Planned enrollment report

	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		
Racial Categories	Female	Male	Female	Male	**Total**
American Indian/ Alaskan Native	0	0	0	0	0
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	2	0	1	3
White	1	3	0	1	5

More than 1 race	0	1	0	0	1
Total	1	7	0	2	10

6) **Study-Wide Recruitment Methods**

Potential participants will be identified using two recruitment methods: 1. Referral by the patient's nephrologist, and 2. DataCore directed search of electronic medical records. Nephrologist referral patients will be obtained from the New York Harbor VA Healthcare System, NYU Langone Health, and Bellevue Hospital. The DataCore directed search of electronic medical records will be limited to patients of nephrologists in the Division of Nephrology who have an episode of mild hyperkalemia in the past 6-months. Once identified using the electronic medical record search, the patient's nephrologists will be notified about their potential eligibility. Per the study inclusion criteria, nephrologists will be asked to confirm that the patient is appropriate for the study.

(a) Dr. Goldfarb or Margaret Curran will review each section of the written consent form with the referred participant, ask the participant if they understand each section, and clarify any questions they may have. The participant and the person obtaining consent will sign and date the consent form. Copies of the consent, which includes the contact information of the PI (Goldfarb), will be provided to the participant and sent to the patient's nephrologist. Informed consent will be considered an ongoing process throughout the study, and participants' questions regarding their rights and responsibilities will be addressed whenever they occur.

(b) Once enrolled, Dr. Goldfarb and Margaret Curran will meet to verify that the participant meets the inclusion/exclusion criteria. This information will be obtained from the patient's electronic medical record.

(c) Study staff will contact eligible patients, and schedule a fasting screening appointment (at least 8 hours of fasting).

A fasting blood sample will be obtained at the screening visit, and analyzed for potassium. If this test is in the range of mild hyperkalemia (potassium 5.1 to <6.5 mEq/L), the participant will be deemed to have persistent hyperkalemia, and be accrued. Otherwise they will be deemed ineligible, and excluded from the study. Regardless of enrollment status, all eligible patients who are invited to participate in the study will be reimbursed $25.00 for time and travel expenses incurred by attending the screening visit.

7) **Study Timelines**

We will recruit 10 participants. Given the intensiveness of the intervention, no more than two participants will be enrolled in the intervention at a time.

8) **Study endpoints**

Among 10 stages 3-4 CKD patients with persistent, mild hyperkalemia, we will evaluate, in a quasi-experimental, controlled feeding study, the efficacy of patiromer for maintaining normal serum potassium concentrations when following a plant-rich diet that includes high-potassium fruits and vegetables, as well as the effects of this diet on health outcomes. The participants will be transitioned gradually to a plant-rich diet, as outlined further below.

The interventions will be evaluated primarily in terms of serum potassium concentrations, but health outcomes will also be assessed, including blood pressure, gastrointestinal symptoms, and fasting concentrations of phosphorus, calcium, magnesium, albumin, glucose, insulin, cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, urea nitrogen, bicarbonate and C-reactive protein. For all parameters, baseline values will be compared to values at the end of each diet phase (weeks 2 and 4).

9) **Procedures involved**

a. Design.

We will conduct an unblinded, quasi-experimental, controlled feeding study, which will be coordinated through the New York University – Health and Hospitals Corporation Clinical and Translational Science Institute (CTSI). Throughout the study, participants will be prescribed patiromer by the study nephrologist (D.S.G.), which will be administered through the CTSI pharmacy. After a 1-week stabilization period, in which participants are prescribed Patiromer while following their usual diets, the feeding component of the study will occur in two phases. During the first phase (week 2), participants will be transitioned to a plant-rich renal diet, which contains moderate protein (10-15% of kcal), restricts dairy products (≤1 serving/day), and eliminates high-potassium fruits and vegetables. During the second phase (weeks 3 and 4), the diet will be altered to provide at-least half of fruits and vegetables from high-potassium sources. To reduce participant burden, meals will be delivered to participants by Portable Chef (New York, NY) three times per week.

i. Patiromer. Patiromer dosing will be determined based on fasting potassium concentrations measured at the end of each week, factoring in both the absolute concentration, as well as the rate of change. The baseline dose of patiromer will correspond to the study by Weir et al. (2015); 8.4-g once per day for participants with a baseline serum potassium of ≥5.1 mEq/L. The following dosing schedule (Table 2) will be used for managing hyperkalemia during the study:

Table 2. Dosing of patiromer during the study based on serum potassium concentrations

Potassium	Change in Potassium	Action
<3.8 mEq/L	Same or decreased	Contact study nephrologist to determine dose
<3.8 mEq/L	Increased	Continue with current dose
3.8-5.0 mEq/L	Changed <0.5 mEq/L	Continue with current dose
3.8-5.0 mEq/L	Changed ≥0.5 mEq/L	Continue with current dose, but notify study nephrologist
5.1-6.0 mEq/L	Decreased	Continue with current dose
5.1-6.0 mEq/L	Same or increased	Contact study nephrologist to determine dose
>6.0 mEq/L	Decreased	Continue with current dose, but notify study nephrologist
>6.0 mEq/L	Same or increased	Contact study nephrologist to determine dose

ii. Research Diets. The guidelines for research diets are outlined in Table 3. With the exception of the Dairy Food Group, diets will be balanced according to the USDA MyPlate. Diets will be based on a 7-day menu cycle, and will be reviewed by participants during the screening visit. In order to promote participant adherence with the diets, participants will be permitted to select appropriate substitutes based on their food preferences from a list of pre-approved substitutes. For example, if a participant does not like to eat apples, they may substitute this for a list of other low-potassium fruits.

Diets will be designed to match a participant's estimated energy requirements based on resting energy expenditure (REE) determined by Mifflin St. Joer equation multiplied by 1.4 to account for thermal effect of food, and physical activity. As a precaution, two small snacks (~100 kcal) that are low in potassium will be provided along with meals, and the prescribed research diet will be adjusted on the subsequent delivery, if needed. Participants will be directed to consume the foods provided, and record any deviations from the prescribed diets. As the intent of the study is not to modify fluid or sodium intake, participants will be encouraged to consume water, and use table salt as per their usual practices. Because coffee and tea are high in potassium, participants will be directed to limit their intake to no more than one cup per day.

Research diet prescriptions will be generated by the study coordinator (M.C.), and prepared and delivered to participants by Portable Chef, a commercial kitchen located in Manhattan that specializes in providing catered meal plans. Meals will be prepared from scratch, using a commercial food scale (TE10FT, Taylor Precision Products, Inc., Oak Brook, IL). Any food items that may undergo commercial processing (e.g., enriched meats) will be carefully selected to ensure that they contain no added sodium, phosphorus or potassium. To ensure the

privacy of participants, staff at Portable Chef will not be provided any participant information, apart from their name, address and phone number, which are necessary to coordinate meal deliveries.

Table 3. Dietary guidelines for research diets

Food Group	Low-K Plant-rich Diet	Liberalized Plant-Rich Diet
Protein Foods	• ¼ animal, ¾ plant	• ¼ animal, ¾ plant
Grain Products	• ½ refined, ½ whole grain	• ½ refined, ½ whole grain
Dairy Foods	• ≤1 serving/day	• ≤1 serving/day
Fruits & Vegetables	• Low-K only	• ½ low-K, ½ high-K

K, potassium

b. Measures. Unless otherwise noted, measurements occur at baseline, and at the end of phase I (week 1) and phase II (week 3). With the exceptions of patiromer dose (obtained from the CTSI Pharmacy) and data obtained from the participant's medical charts, study measurements will be obtained during visits to the CTSI Clinical Research Center (CRC) at Bellevue Hospital. A summary of study visits and procedures is provided at the bottom of this section (Table 4).

i. Screening measurements. At the screening measurement visit, a fasting blood sample will be collected and analyzed for serum potassium concentrations. In addition, height and weight will be measured by study staff at the CTSI using a stadiometer and balance scale, respectively for estimating energy requirements (see 9.ii.)

ii. Baseline measurements. In addition to the outcome measures (described in detail below), key information used to characterize the patient population and/or control for as covariates, will be collected at baseline through questionnaires, review of patients' medical charts and clinical measurements. Questionnaires will be self-administered, and will include questions on diagnosis with diabetes and hypertension, race/ethnicity, sex, age, income, education, employment, tobacco and alcohol use, use of dietary supplements and urine output. Data collected from medical charts will include cause of CKD, diagnosis of diabetes and hypertension (for comparison to and verification of self-report), urine albumin concentration, prescriptions for vitamin D, antihypertensives, hypoglycemic agents, insulin, and phosphorus binders. Variables that may change during the intervention, including body weight and medications, will also be assessed at the end of phase I (week 2) and phase II (week 4).

ii. Usual dietary intake. Usual dietary intake of participants will be assessed during the stabilization period (week 1). Participants will be asked to maintain a 3-day food record, which includes two weekdays, and one weekend day. Food records will be reviewed with the study coorindator (M.C.) at the end of the stabilization period to ensure accuracy.

iii. Serum potassium concentrations. The primary purpose of this study is to evaluate the efficacy of patiromer for maintaining serum potassium concentrations in CKD patients during transition to a liberalized plant-rich diet by comparing fasting serum potassium concentrations at screening to values at the end of phase I (week 2) and phase II (week 4) of the study. However, because potassium concentrations are also being used to titrate the dose of patiromer needed to achieve normal potassium concentrations, fasting serum potassium concentrations will also be measured at the end of weeks 1 and 3. To ensure a rapid response to changes in serum potassium concentrations, blood samples obtained at the CTSI CRC will be immediately delivered to the study laboratory at Tisch Hospital for analysis, and the results sent to the CTSI Pharmacy for evaluation (section 10.a.i.). Participants will be directed to pick up new prescriptions from the CTSI Pharmacy on the days of measurement. To obtain a measurement of serum potassium concentration, a 0.5 mL sample of blood is required.

iv. Blood pressure. Systolic and diastolic blood pressures will be measured after 5-minutes of rest in a seated position with their arm supported at the level of their heart and their feet resting of the floor using an automatic sphygmomanometer. Blood pressure measurements will be obtained in duplicate with a third measure obtained if the systolic or diastolic values on repeated measurement differ by more than 5 mmHg.

v. Gastrointestinal symptoms. The frequency and severity of participant gastrointestinal symptoms in the previous week (abdominal cramping, abdominal discomfort, indigestion, infrequent or difficult to pass bowel movements, flatulence, loose or watery stools) will be self-reported via an investigator-developed questionnaire at baseline, and at the end of the stabilization period (week 1), phase I diet (week 2), and phase II diet (week 4).

vi. Other biochemical parameters. Fasting blood samples will be obtained at the CTSI CRC, and analyzed for concentrations of phosphorus, calcium, magnesium, albumin, glucose, insulin, cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, urea nitrogen, bicarbonate and C-reactive protein. Similar to serum potassium concentrations, blood samples will be delivered by study staff to the laboratory at Tisch Hospital for analysis. To obtain these biochemical measurements, approximately 5.0 mL of blood is required.

Table 4. Summary of study visits and procedures

	Screening	Baseline	Wk 1	Wk 2	Wk 3	Wk 4
Baseline Questionnaire (comorbidities, sociodemographics, tobacco and alcohol use, use of dietary supplements and urine output)		X				
Medical Chart Review (cause of CKD, comorbidities, urine albumin concentration)		X				
Medical Chart Review (medications)		X		X		X
Dietary Assessment (3-day food record)			X			
Anthropometrics (height)	X					
Anthropometrics (weight)	X			X		X
Fasting Blood Test (potassium)	X		X	X	X	X
Fasting Blood Test (phosphorus, calcium, magnesium, albumin, glucose, insulin, cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, urea nitrogen, bicarbonate and C-reactive protein)		X		X		X
Blood Pressure (systolic and diastolic blood pressure)		X		X		X
Gastrointestinal Symptoms Questionnaire (frequency and severity of abdominal cramping, abdominal discomfort, indigestion, infrequent or difficult to pass bowel movements, flatulence, loose or watery stools in previous week)		X	X	X		X

10) **Data and Specimen Banking**

No samples will be stored for future analyses in this study.

11) **Data Management**

Information to be obtained from participants includes height and weight, blood pressure, medical history, blood tests, and self-administered questionnaires (sociodemographics, clinical and comorbid conditions/ management, cigarette and alcohol use and gastrointestinal symptoms). None of the data to be collected is considered sensitive in nature. Some of the participant data such as laboratory results will be linked to the participant's name. Other data (e.g., height, weight, blood pressure, medical history, and surveys) will be linked to the participant through a subject ID number. As a further measure to protect participants' privacy, different subject ID numbers will be used for study measurements and for coordinating the feeding component of the study. We will maintain separate files for identified and de-identified data in locked file cabinets in a locked office. Access to these data will be restricted to the PI (Goldfarb), and study staff responsible for gathering data and maintaining research files. Data will be entered into a centralized database maintained on a secure server. Data

in these files will be linked to participants only through their ID number – this file will be maintained in a locked filing cabinet at 180 Madison Avenue. All data collected will be used expressly for the purpose of the proposed study.

a. Overview.

A descriptive analysis of all data collected will be performed using appropriate graphical and numerical exploratory data techniques. The information obtained from this preliminary investigation of the data will be used to: (1) assess data quality and completeness, (2) describe univariate distributions at baseline and follow up, and (3) create summary statistical data for outcome variables at each time point, including the proportion of participants with hyperkalemia. We will identify features of the data that may necessitate special analytic methods (e.g., excess zeros, missing data, departures from distributional assumptions, outliers).

For analytic analyses, we will examine: (1) changes in outcome variables (blood pressure, gastrointestinal symptoms, and fasting concentrations of potassium, phosphorus, calcium, magnesium, albumin, glucose, insulin, cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, urea nitrogen, bicarbonate and C-reactive protein), and covariates (weight, medications, dose of Patiromer) between baseline and the end of each diet phase, and (2) relationships between the changes in outcome variables and covariates. Changes in study outcomes will be will be graphically depicted using means $\pm$ SD or median (IQR) as measures of central tendency and variance. Changes in study outcomes will be analyzed using repeated-measures analysis of variance with post-hoc Tukey HSD test. Because of the small sample size, covariates will be reported instead of being included in a multivariable model. Depending on the types of covariate and outcome of interest, subgroup analyses may be performed with these participants removed from the dataset. For example, if a participant's dose of phosphorus binder medications changed during the study, the analysis of phosphorus concentrations would be conducted with/without this participant. Given the short during of this study (4 weeks) in relation to typical monitoring of patients with stage 3B-4 CKD, we expect that that few, if any, subgroup analyses will be required.

12) **Provisions to Monitor the Data to Ensure the Safety of Subjects**

Protection against Risk.

Once half of the participants are enrolled and accrued, the PI (Goldfarb) will review serum potassium concentrations to ascertain if there were any episodes of moderate-severe hyperkalemia, or protocol issues that require reporting, withdrawing a participant and/or stopping the study. An AE is any unfavorable and unintended sign, symptom, or disease, including worsening of pre-existing medical conditions. The criteria for withdrawing participants are outlined in section 14 below. The study will be stopped if there is a serious adverse events (SAE) related to the study. Any SAE related to the intervention will be reported to the NYU School of Medicine Institutional Review Board by phone and email within 24-hours of being notified. To minimize participant risk and facilitate monitoring, we plan to enroll cohorts of $\leq$2 participants rather than a single cohort of 10 participants. Summary data and safety monitoring reports will be submitted to the NYU School of Medicine Institutional Review Board during annual review, or if there are changes in the risk/benefit ratio of the study.

As per our Clinical Trial Agreement with Relypsa, Inc., the PI will undergo training in reporting AEs by Relypsa, Inc. before starting the study, and will report all AEs that occur after the signing of informed consent, and up to 14 days after the intervention to the Drug Safety and Pharmacovigilance (DSPV) Department at Relypsa, Inc within 15 days of completing the study. Any AEs that are considered serious (SAEs), which occur will be reported to Relypsa, Inc. DSPV Department within 24-hours of being identified/reported. SAE include "any untoward medical occurrence that at any dose: (i) results in death; (ii) is immediately life threatening (i.e. in the opinion of the investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death); (iii) requires inpatient

hospitalization or results in prolongation of an existing hospitalization; (iv) results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; (v) is a congenital anomaly or birth defect; or (vi) is an important medical event that may not be immediately life threatening, result in death, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed in subsections (i) – (v)" (defined per the Clinical Trial Agreement with Relypsa, Inc.).

This study investigates the use of patiromer for managing normal serum potassium concentrations in CKD patients who are transitioned to a plant-rich diet. The major risk to participants in this study is cardiotoxicity related to hyperkalemia. Patiromer has been demonstrated to be effective for lowering serum potassium concentrations and keeping them in the normal range in CKD patients with hyperkalemia, but the role of dietary potassium on serum potassium concentrations is unclear. Current dietary guidelines for managing hyperkalemia in CKD patients recommend avoiding high-potassium plant foods; however, this long-standing practice has never been demonstrated to be necessary, and may contribute to other disease complications[4]. To our knowledge, this is the first study to evaluate liberalizing the diets of CKD patients with hyperkalemia, so we have incorporated many design features that can help us to protect against this risk.

Prior to the intervention, participants will receive education on the signs and symptoms of hyperkalemia; muscle weakness, abnormally slow or rapid heart rate, and heart palpitations (from Patient education: Hyperkalemia (the basics); UpToDate.com)[6]. Participants will be directed to monitor themselves for these conditions, and to go to the emergency room if they start experiencing them, making sure to notify the emergency department staff about their participation in the study. Standard treatment for acute episodes of hyperkalemia includes intravenous infusions of calcium gluconate and glucose/insulin, often followed by polystyrene sulfonate or emergent dialysis to remove excess potassium. The emergent treatment of adverse events will be at the discretion of the attending physician. In the event of any admission to the emergency room (even if determined to be unrelated to hyperkalemia), participants will be asked to alert the study PIs as soon as possible.

The intervention contains several features to lower the risk of hyperkalemia. For one, the research diets will be prepared for participants to provide control over the dietary potassium exposure. We will use the feeding study approach that gradually increases dietary potassium in a step-wise manner in order to prevent large shifts in dietary potassium intake. During phase I, participants will be stabilized on a plant-rich diet that restricts dairy products and excludes fruits and vegetables that are high in potassium. This closely approximates the current dietary recommendations for CKD patients with hyperkalemia, but does include plant-based foods from the Protein Foods Group (legumes, nuts, seeds), which are high in potassium (>200 mg/serving). However, compared to the typical Western diet, plant-rich diets are more alkaline, and are higher in fiber, factors that are thought to help control serum potassium concentrations[4]. After a week of consuming this diet, high-potassium fruits and vegetables will be introduced, and make up half of the fruit and vegetable servings. We will closely monitor participants' adherence to the research diets through daily food records to ascertain their adherence with the study diets – participants that are determined to be non-adherent with the research diets at the end of phase I (defined in section 14) will be withdrawn from the study.

Another intervention feature to lower the risk of hyperkalemia is the close monitoring of participants' serum potassium concentrations to adjust the dose of patiromer (10.a.i. Table 2). We will measure serum potassium concentrations as per current patiromer recommendations (weekly), and samples will be processed through the Tisch Laboratory, and the results sent to the CTSI Pharmacy for review. If values are abnormally high or rapidly increasing towards hyperkalemia (10.a.i. Table 2), the study nephrologist (D.S.G.) will be immediately contacted. Because hemolysis can cause artificially elevated serum potassium values, participants with abnormally high or rapidly increasing concentrations of serum potassium will have another blood test to confirm their serum potassium concentrations.

In addition to risks associated with hyperkalemia, there are potential risks related with patiromer use. In a sample of 734 patients treated with patiromer, the most common AEs were constipation (7.2%), hypomagnesemia (5.3%), diarrhea (4.8%), nausea (4.8%), abdominal discomfort (2.0%) and flatulence (2.0%). It is likely that the most common of these AEs (constipation, hypomagnesemia, diarrhea) would be attenuated by a plant-rich diet, which contains higher amounts of fiber and magnesium compared to the typical Western diet. The less common adverse events (abdominal discomfort, flatulence) may be exacerbated by the higher intakes of dietary fiber. These potential AEs will be assessed at the end of each week through the gastrointestinal symptoms questionnaire, and blood testing at the end of phase I and II (for hypomagnesemia). Patiromer also has the potential to bind to other medication, reducing their absorption. This will be mitigated by directing patients to take patiromer once daily, and at least 3 hours away from other medications.

It is unlikely that women and men with stages 3-4 CKD will become pregnant or impregnate someone. Additionally, we will exclude anyone who is planning on becoming pregnant from the study. As part of our Clinical Trial Agreement with Relypsa, Inc., we will report any pregnancies (whether female or male impregnating a female) to Relypsa, Inc. In addition, because the patiromer and the research diets are untested in pregnant women, we will withdraw women who become pregnant during the study period.

Lastly, participants in the study are at risk of breaches of confidentiality. A variety of measures will be used to prevent breaches of confidentiality. First, all study staff will be trained in the NYULMC Practice Fundamentals, which include training in issues of confidentiality. Additionally, all study staff will be required to sign a confidentiality agreement. Although study staff may have access to sensitive information about the participant as recorded in their medical record, only that information pertinent to the study outcomes will be abstracted from the medical record. Data will be maintained as described above (see section 12). We will take steps to avoid participants' perceptions of coercion in the recruitment process.

13) **Withdrawal of subjects**

As mentioned previously, participants may be withdrawn from the study without their consent in the event that they become pregnant, or they are non-adherent with the research diets. Non-adherence to the research diets will be defined as consumption of >25% of energy from non-research diet foods, which will be assessed at the end of phase I of the study. In the event that involuntary withdrawal is required, participants will be referred back to their treating physician of record for evaluation and management. Data collection will cease at the time of withdrawal.

14) **Risks to subjects**

Most of the risks associated with this study are outlined in section 13 along with corresponding measures to protect against these risks (include hyperkalemia, patiromer side effects and interactions with medications, and breach of confidentiality). Blood tests will be drawn for this study, which are sometimes accompanied by bruising, bleeding, and minor tenderness at the puncture site. Participants will be made aware of all of these risks prior to enrolling in this study.

15) **Potential Benefits of the Proposed Research to the Subjects and Others**

Participants may experience some temporary improvement in cardiometabolic risk factors and serum potassium concentrations related to intervention; however, this is not guaranteed. Moreover, any temporary improvements in these conditions are unlikely to have any lasting benefits to participants.

This study will not provide the investigators with data to demonstrate improvements in health-related quality of life, morbidity, mortality, and utilization or cost of care. However, if proven efficacious, future CKD patients may benefit from the knowledge generated from this study regarding the need to limit or avoid high-high-potassium plant foods, and the potential health benefits of a plant-rich dietary pattern. Because this is a

proof-of-concept study, the emphasis has been placed on safety and internal validity rather than real-world applicability and generalizability to the CKD population. Consequently, this is just a first step in several needed to benefit future CKD patients. Additional longer-term studies in free-living CKD patients would be needed before any such changes in practice could be realized.

16) **Vulnerable populations**

No vulnerable populations are included in this study.

17) **Multi-site research**

Not applicable.

18) **Community-based participatory research**

Not applicable.

19) **Sharing results with subjects**

The study results will not be shared with participants who will be expected to return to usual care practices upon completion of the study.

20) **. Setting**

Research activities will occur at the CTSI CRC and Renal Clinic of the New York VA. Ethical review will be obtained from the Institutional Review Board at NYULMC.

21) **Resources available**

i). Personnel.

INVESTIGATORS

David Goldfarb, MD (Principal Investigator, Effort = 0.6 CM) is a Professor in the Departments of Medicine and Neuroscience and Physiology at the New York University School of Medicine, and Chief of Nephrology at the Renal Clinic of the New York VA. He is a nephrologist with extensive clinical and research experience with individuals with chronic kidney disease, including trials of medications. He is well- known in the local nephrology community. Dr. Goldfarb is co-investigator to Dr. Sevick's ongoing Diabetes Healthy Hearts study (R01), and pending Kidneys and Behavioral Management of Phosphorus study (R21). He will provide crucial medical oversight to the study, in particular safety monitoring, patiromer prescriptions, and assist with interpretation of data from a medical perspective in the dissemination of study results. Dr. Goldfarb has a part-time university position and his effort is estimated as a function of his university appointment.

Mary Ann Sevick, ScD, RN, (Co-Investigator. Effort = 0.6 CM) is a Professor in the Department of Population Health at New York University School of Medicine, and Director of the mHealth Unit in the Center for Healthful Behavior Change. Over the past 20 years, Dr. Sevick has had experience with a variety of large clinical trials. Her primary interest is in the area of chronic illness and she has recently been involved, as principal investigator, in several studies to examine disease management regimens. She recently completed the BalanceWise study (NIH-R01-NR010135), a randomized clinical trial to evaluate the efficacy of a behavioral intervention to reduce sodium intake in hemodialysis patients, and is currently the principal investigator of the NIDDK-funded Diabetes Healthy Hearts and Kidneys Study R01, a clinical trial evaluating alternative uses of technology to change multiple behaviors in those with diabetes and concurrent stage 2-4 chronic kidney disease. As an experienced clinical investigator in the Center for Healthful Behavior Change, Dr. Sevick will work closely with Dr. Goldfarb to manage the proposed project.

Simon Jones, PhD MSc (Co-Investigator, Effort = 0.6 CM) is a Research Professor in the Department of

Population Health at the New York University School of Medicine at the University. Dr. Jones has extensive experience in data management and statistical analysis. As such, he will oversee generation of preliminary reports for data quality, safety, and recruitment. In addition, he will review all analyses specified in the proposal, and assist with interpretation of these analyses in the dissemination of study results.

OTHER PERSONNEL

Margaret Curran, (Research Coordinator, 0.6 CM). The research coordinator will work with staff at the New York Harbor VA Healthcare System and CTSI-CRC. She will be responsible for conducting screening, baseline and follow up measurement visits, reviewing participant's medical charts for eligibility, obtaining informed consent, and coordinating study visits.

ii). Institutional setting.

Renal Clinic at the New York Harbor Veterans Affairs Healthcare System: The Renal Clinic at the New York Harbor VA Healthcare System serves approximately 250 CKD patients in the Greater New York City region, and will be the source population for this study. The electronic medical records system at the New York VA Healthcare System will be used to assist in identifying potentially eligible patients for the study, and for obtaining clinical information to describe the patient population.

Department of Population Health, NYULMC: The Department of Population Health, within NYUSOM, aims to integrate, support, and advance NYULMC's contributions to population health research and related disciplines, providing a vibrant departmental home for the "bedside-to-population" as well as the "population-to-discovery" domains of translational research. It provides an academic base for efforts to integrate research into NYU's expanding health care delivery system that transcends any particular school, department, or division. The Department is a research and training hub that brings together researchers in nursing, medicine, psychology, epidemiology, biostatistics, health services and policy, behavior change, comparative effectiveness, medical ethics, prevention, and related disciplines, affording a unique and collaborative environment focused on improving the health of populations. The Department was initiated in January 2012. A core focus of the Department is improving health outcomes through innovative interventions as well as in enhancing the impact of interventions already known to be effective through their more effective implementation and dissemination. Collaboration with key public sector stakeholders and with community partners is central to the Department's mission. As researchers, faculty are engaged in dual roles: building cutting-edge science in their areas of inquiry, and providing collaborative consultation to other investigators throughout the NYULMC academic community as well as across the University. Resources within the Department for this proposal include the use of over 5,000 square feet of dedicated office space located on the newly renovated 6th floor of the NYULMC Translational Research Building, telecom (phone, fax and LAN connections), administrative assistants, and grant, regulatory (IRB) and finance administrators.

Center for Healthful Behavior Change, NYULMC: The Center for Healthful Behavior Change (CHBC) is located within the Department of Population Health. The mission of CHBC is to become a national leader in translational behavioral medicine, research, training, and education. The CHBC works toward this mission through the development, implementation, and dissemination of innovative evidence-based behavioral interventions in routine clinical practice and community-based settings with the long-term goal of disseminating effective strategies nationally and internationally. The Center is comprised of core research faculty members with expertise in various fields relevant to translational behavioral research. Faculty engage in research pertaining to heart disease, hypertension, chronic kidney disease, diabetes, cancer, health disparities research, community-based participatory research, health psychology, behavioral informatics, and health education and counseling.

Division of Biostatistics NYULMC: Dr. Jones' office is 180 Madison Avenue, in the same building as the study coordinator (M.C.). Dr. Jones has access to state-of-the-art computing facilities that include a central server (Dell PowerEdge 2500) and a Sun Server. Statistical software available either on the network or the

desktop includes SAS, SPSS, S-Plus (including Spatial Stats and Environmental Statistics Modules), R, PASS and Matlab.
Portable Chef: Portable Chef is a metabolic kitchen / foodservice vender that will carry out the critical task of preparing meals and snacks for the study. This responsibility includes developing menus based on the pre-defined dietary patterns, sourcing ingredients, preparing and weighing foods and beverages, and delivering them to the participants to consume. The project study dietitian (D.E.S.) reviewed available foodservice operations in the Greater New York City area, and selected Portable Chef for this intervention based on their capacity, delivery, and experience in developing and preparing tailored, weighed menus for researchers and clients with special food requirements.

22) **Prior approvals**

We have received approval from the Chief of the Nephrology at the New York Harbor VA Healthcare System to coordinate this study in their Renal Clinic. We also have approval from Portable Chef Director (Uri Attia), and a vendor agreement with Portable Chef is already in place for prior research projects.

23) Subject Payments

Potential participants will be paid $25.00 for the screening visit, and enrolled participants will additionally receive $25.00 per visit to the CTSI CRC.

24) **Local number of subjects**

We will recruit a total of 10 individuals to the study. Preliminary data from the New York Harbor VA Healthcare System indicate that we will have access to approximately 250 patients with CKD, ~10% of which have hyperkalemia.

25) **Confidentiality**

Some of the participant data such as laboratory results will be linked to the participant's name in their medical chart. Other data (e.g., surveys) will be linked to the participant through an ID number. We will maintain separate files for identified and de-identified data in locked file cabinets in a locked office. Access to these data will be restricted to the PI (Goldfarb), and study staff responsible for gathering data and maintaining research files. Data will be entered into a centralized database maintained on a secure server. Data in these files will be linked to participants only through their ID number. All data collected will be used expressly for the purpose of the proposed study.

26) **Provisions to Protect the Privacy Interests of Subjects**

Measures to be used to protect subjects' privacy interests are described in section 13 above. Data collection will occur at the New York Harbor VA Healthcare System (for medical chart review), CTSI Pharmacy (for patiromer dose), and CTSI CRC (questionnaires, anthropometric and clinical measurements, blood tests). Measurements at the CTSI will be conducted in private rooms. Participants will be told that they can refuse to respond to any questions that make them uncomfortable, and that they can withdraw from the study at any time.

27) **Compensation for research-related injury**

Participants will not be compensated for research-related injuries.

28) **Economic burden to subjects**

Neither the patient nor the patient's health insurance will be billed for any study activities (including research diets), tests, or procedures related to the study. The cost of all procedures and tests will be covered by funds

received from Relypsa, Inc.

29) **Consent process**

A brief description of the study will be provided at the time of screening for the study. After reviewing the consent form with patients, and after they have signed the consent form, we will verify that they meet the inclusion/exclusion criteria (sections 5.i and 5.ii.). Potential participants will be shown the research diet menus to determine whether they are willing and able to adhere to the research diets. All questions will be answered.

A copy of the consent form will be given to the participant and they will be encouraged to contact the PIs with any and all questions that occur at any time during the conduct of the study. No patients will be excluded on the basis of race/ethnicity, but this pilot study has a sample size that is insufficient to examine differences in the intervention by race/ethnicity.

30) **Process to document consent in writing**

Patient's consented participation in this study will be documented in their medical record.

31) **Drugs or devices**

Participants in this study will be prescribed patiromer (dosing 10.a.i. Table 2), under the supervision of the study nephrologist (D.S.G.). Patiromer is an FDA-approved cation-exchange polymer that binds to potassium in the digestive tract, and is excreted (along with bound potassium) in feces. Patiromer is indicated for the treatment of hyperkalemia, and is demonstrated to result in clinically significant reductions in serum potassium concentrations. The safety concerns associated with patiromer, along with measures to reduce these complications, are noted in section 13, and include constipation (7.2%), hypomagnesemia (5.3%), diarrhea (4.8%), nausea (4.8%), abdominal discomfort (2.0%) and flatulence (2.0%), and binding to other medications.

References.

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4. St-Jules DE, Goldfarb DS, Sevick MA. Nutrient non-equivalence: Does restricting high-potassium plant foods help to prevent hyperkalemia in hemodialysis patients? J Ren Nutr 2016;26(5):282-287.
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6. UpToDate®. Patient education: Hyperkalemia (the basics). UpToDate website. https://www.uptodate.com/contents/hyperkalemia-the-basics?source=see_link. Accessed February 20, 2017.