IRB protocol with statistical analysis plan

Title: Comparison of Potassium Binders in the ER

NCT number: NCT04585542

Document date: 2 April, 2021

UCI Office of Research	**Institutional Review Board** **Human Research Protections** **Protocol Narrative – Expedited/Full Committee Biomedical/Clinical Research** *Version June 2020*
Upload this completed narrative and any supplemental documentation to the IRB Application.	**IRB USE ONLY –** **HS#: 2020-5780**
Lead Researcher Name: Wei Ling Lau, MD	
Study Title: Potassium Binders in the Emergency Department	

CLINICAL TRIAL MASTER PROTOCOL AND INVESTIGATIONAL BROCHURE INFORMATION *

	Master Protocol	Investigator Brochure: <Specify Drug/Device>	Investigator Brochure: <Specify Drug/Device>	Sponsor Consent Form Template(s)
Version #:				
Version Date:				

[X] This study is investigator-authored (investigator developed the study and is conducting the study at UCI and/or with other non-UCI sites).

* Add columns as applicable

NON-TECHNICAL SUMMARY

Provide a brief non-technical summary or synopsis of the study that can be understood by IRB members with varied research backgrounds, including non-scientists and non-affiliated members.

Hyperkalemia is defined as an elevated blood potassium. Hyperkalemia can be dangerous if it disrupts normal heart rhythm, and can cause sudden death. It presents a significant public health burden; patients presenting to the Emergency Department (ED) with hyperkalemia have a 4 times higher rate of hospital admissions, and 7 times longer average length of hospital stay. In the past 5 years there have been 2 new medications released on the market (patiromer and zirconium) that work to lower potassium through the intestinal tract, via elimination in the stool. These newer medications have not been compared head-to-head with the old medication (sodium polystyrene sulfonate) and their utility in the management of acute hyperkalemia is unknown.

The purpose of this study is to compare the efficacy of different potassium-lowering medications in ED and hospital patients presenting with acute hyperkalemia. We are primarily interested in the degree of potassium lowering at 2 hours and 4 hours. We will also compare subsequent length of hospital stay after treatment with each potassium-lowering medication. The data from our study will be important

toward informing medical guidelines for the treatment of acute hyperkalemia.

SECTION 1: PURPOSE AND BACKGROUND OF THE RESEARCH

1. Provide the scientific or scholarly rationale for the research. Describe the relevant background information and the specific gaps in current knowledge that this study intends to address.

The purpose of this research study is to determine the effects of various potassium binders (sodium polystyrene sulfonate, patiromer, zirconium) vs control (non-specific laxative such as Miralax) in ED and hospital patients found to have elevated blood potassium > 5.5 mEq/L. Hyperkalemia is a fairly common electrolyte disorder with varying levels of severity. Normal range for potassium is 3.3-4.8 mEq/L at UCI Health. Moderate hyperkalemia is in the range 5.5-5.9 mEq/L while severe hyperkalemia is ≥6.0 mEq/L or if patient is symptomatic: muscle weakness/paralysis or with EKG changes (e.g., peaked T waves, widening QRS, arrhythmias including ventricular fibrillation or asystole). Hyperkalemia is most commonly associated with kidney insufficiency, metabolic acidosis, and the use of medications such as renin-angiotensin-aldosterone system inhibitors.

In an emergency, the main goal is to reverse adverse cardiac effects and shift potassium into cells using interventions such as insulin/glucose and albuterol. However, these are only temporary measures. To remove potassium from the body, agents or interventions that may be used include cation exchange resins (potassium binders), loop diuretics, or dialysis. For over 50 years the only available oral cation exchange resin has been sodium polystyrene sulfonate. In recent years, two new agents (patiromer and zirconium) have been approved by the FDA for chronic management of hyperkalemia.

The cation exchange resins have not been studied head-to-head in the acute setting. This is a *critical knowledge gap* since acute hyperkalemia poses a significant burden on the healthcare system. In claims data analysis of 80,000 patients, half with hyperkalemia and half without, the patients with hyperkalemia had 4 times higher rate of inpatient admissions, 7 times longer average length of stay, and 30-day hospital readmission rate 14.21% vs 9.86% in the non-hyperkalemia cohort (Kidney Int Rep. 2017 Nov 14;3(2):385-393). The findings from our study will help inform decision-making guidelines for the treatment of acute hyperkalemia.

2. Provide relevant preliminary data (animal and/or human).

Sodium polystyrene sulfonate (SPS): No original randomized controlled trial (RCT) in acute hyperkalemia. available to evaluate efficacy. A small double-blind RCT in 33 patients with CKD stage 3-5 evaluated SPS 30g daily vs placebo x7 days, in mild hyperkalemia (potassium level 5-5.9 mEq/L). SPS was superior to placebo in the reduction of serum potassium levels (mean difference between groups, -1.04 mEq/L; 95% CI, -1.37 to -0.71, p<0.001). There was a trend toward higher rates of electrolyte disturbances and an increase in GI side effects with SPS therapy (Lepage et al. CJASN. 2015; 10(12):2136-2142). Bowel necrosis, although rare, is a concern with sodium polystyrene sulfonate and may discourage some medical providers from utilizing this drug.

Patiromer: Patiromer was studied in a two-part, single-blind randomized withdrawal study that evaluated hyperkalemic patients with CKD stage 3-4 on stable doses of at least one RAAS-inhibitor. In Part A, 243 patients were treated with patiromer for 4 weeks; in patients who had starting potassium level of 5.5 to <6.5 mEq/L group, potassium decreased by -1.23 +/- 0.04 (95% CI: -1.31,-1.16, p<0.001). In Part B, 107 patients were randomized to continue patiromer or to receive placebo. Serum potassium rose by 0.72 mEq/L in patients who were switched to placebo versus no change in patients who remained on patiromer (p<0.001) (Weir et al. NEJM. 2015;372:211-221).

Sodium Zirconium Cyclosilicate: Zirconium was compared to placebo in a RCT of patients with serum potassium level 5-6.5 mEq/L. Approximately 60% of patients had chronic kidney disease, 10% had heart failure, 62% had diabetes mellitus, and 67% were on RAAS inhibitor therapy at baseline. At 48 hrs, the 2.5, 5, and 10 g zirconium dose showed a mean reduction in potassium of 0.5, 0.5, and 0.7 mEq/L respectively. The study was further carried out to 12 days, and demonstrated effective maintenance of potassium control with the 5 and 10 g doses when compared with placebo. Rates of adverse events were similar in the zirconium and placebo group (12.9% and 10.8% respectively with acute therapy). Diarrhea was the most common complication (Packham et al. NEJM. 2015; 372:222-231).

A recent review paper concluded that patiromer and zirconium induce a more predictable reduction in potassium concentration and demonstrate an improved safety profile over SPS. From review of small trials, the authors report that onset of action for SPS was variable between 2-6 hours; for patiromer was 7 hours; and for zirconium can be as short as 1 hour depending on the dosage. The data was limited by inclusion of patients with mild-moderate hyperkalemia, thus data is lacking in patients with more significant potassium elevations (Beccari & Meaney Core Evid. 2019 Feb 27;14:1).

3. Describe the purpose, specific aims or objectives. Specify the hypotheses or research questions to be studied.

The purpose of this study is to compare the efficacy of different oral potassium binders in ED and hospital patients presenting with acute hyperkalemia.

Specific Aim 1: To compare a nonspecific laxative, SPS, patiromer and zirconium in the treatment of acute hyperkalemia.
Hypothesis 1: Zirconium will be the most effective agent for lowering of blood potassium, and will be associated with shorter hospital stay.

Specific Aim 2: To compare side effects with the different potassium binders.
Hypothesis 2: GI side effects will be similar between the various potassium binders. Patients will rate the newer agents patiromer and zirconium more favorably in terms of palatability.

4. Describe the primary outcome variable(s), secondary outcome variables, and predictors and/or comparison groups as appropriate for the stated study objectives/specific aims.

While monitoring change in blood potassium level, we will also track changes in calcium, magnesium and phosphorus since nonspecific cation binding may occur. Zirconium can induce mild sodium

loading since it exchanges sodium for potassium, thus we will evaluate changes in blood pressure and patient-reported leg edema. The 4 comparison groups are as follows (potassium binders will be added to standard of care):

1. Nonspecific laxative (MiraLAX)
2. SPS 30 g
3. Patiromer 25.2 g
4. Zirconium 15 g

Primary end-points:
Change in serum potassium at 2 and 4 hours
Length of ED or hospital stay
Admit to hospital yes/no

Secondary end-points:
Dialysis yes/no within 8 hours
Change in calcium, phosphorus and magnesium
Change in blood pressure
New lower extremity edema
Palatability (patient subjective rating)

5. List up to ten relevant references/articles to support the rationale for the research. Do not append an extensive NIH-grant-style bibliography.

1. Beccari, M., & Meaney, C. (2017). Clinical utility of patiromer, sodium zirconium cyclosilicate, and sodium polystyrene sulfonate for the treatment of hyperkalemia: an evidence-based review. *Core Evidence*, *Volume 12*, 11–24.
2. Malone, D. J. (2015). Taking a Second Look at Kayexalate. *Hospital Pharmacy*, *50*(11), 959–960.
3. Lepage, L. et al. (2015). Randomized Clinical Trial of Sodium Polystyrene Sulfonate for the Treatment of Mild Hyperkalemia in CKD. *CJASN*, 10(12):2136-2142
4. Leon, S. J. et al. (2019). New therapies for hyperkalemia. *Current Opinion in Nephrology and Hypertension*, *28*(3), 238–244.
5. Anker, S. D. et al. (2015). Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: results from a phase 3 randomized, double-blind, placebo-controlled trial. *European Journal of Heart Failure*, *17*(10), 1050–1056.
6. Bakris, G. L. et al. (2015). Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease. *JAMA*, *314*(2), 151.
7. Packham, D. K. et al. (2015). Sodium Zirconium Cyclosilicate in Hyperkalemia. *NEJM*; 372:222-231.
8. Weir, M. R. et al. (2017). Effectiveness of patiromer in the treatment of hyperkalemia in chronic kidney disease patients with hypertension on diuretics. *Journal of Hypertension*, *35*, S57–S63.
9. Betts, K. A. et al. (2017) The Cost of Hyperkalemia in the United States. *Kidney Int Rep*, 3(2), 385-393.

SECTION 2: ROLES AND EXPERTISE OF THE STUDY TEAM

1. **List the Lead Researcher and Co-Researchers who will engage in human subject research.** *Co-Researchers are faculty, staff, students and other academic appointees who the Lead Researcher (LR) considers to be key personnel for conducting the research study. These individuals work closely with the LR to design, conduct, and/or report on the research.*
2. ***UPDATED!*** **List Research Personnel as required per the Research Personnel Heat Map.**
3. **In lieu of listing Research Personnel (as required per the Research Personnel Heat Map), the LR must maintain the Study Team Tracking Log (or something similar) listing all Research Personnel who are engaged in the research.**
4. For each research team member, indicate all applicable research activities the individual will perform. *Finalizing informed consent is reviewing, answering/asking questions, confirming competency, as necessary, and signing/confirming the informed consent.*
5. If applicable, list the Faculty Sponsor as a Co-Researcher who will have research oversight responsibilities.

Lead Researcher:

Name and Degree: Wei Ling Lau, MD

Position/Title and Department: Assistant Professor in Medicine, Division of Nephrology

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Lau has experience being site PI for trials in dialysis patients. She will be involved in oversight of research activities, assist with patient recruitment, and ensure completeness of data collection and analyses.

Co-Researcher:

Name and Degree: Kamyar Kalantar-Zadeh, MD PhD

Position/Title and Department: Professor in Medicine, Chief of Division of Nephrology

Team Member will: **[ ]** serve as Faculty Sponsor with research oversight responsibilities

[ ] Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[ ]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Kalantar-Zadeh has been involved in human subjects research for >15 years and is currently PI on a NIH-funded investigation of dietary effects in dialysis patients. He will advise on trial design and data analyses.

Co-Researcher:

Name and Degree: Shahram Lotfipour, MD MPH

Position/Title and Department: Professor in Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Lotfipour has extensive experience with clinical trials in the Emergency Department. He will assist with patient recruitment and advise on data collection and analyses.

Co-Researcher:

Name and Degree: Lawrence Nguyen, DO

Position/Title and Department: Fellow, Division of Nephrology

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Nephrology fellow Dr. Nguyen will participate in patient recruitment, data collection and data analysis.

Co-Researcher:

Name and Degree: Sam Tonthat, DO

Position/Title and Department: Fellow, Division of Nephrology

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Nephrology fellow Dr. Tonthat will participate in patient recruitment, data collection and data analysis.

Co-Researcher:

Name and Degree: Brian Wang, DO

Position/Title and Department: Fellow, Division of Nephrology

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Nephrology fellow Dr. Wang will participate in patient recruitment, data collection and data analysis.

Co-Researcher:

Name and Degree: Ramy Hanna, MD

Position/Title and Department: Assistant Professor, Division of Nephrology

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Hanna is a site PI on a separate ongoing clinical trial at UCI. He will participate in patient recruitment, data collection and data analysis.

Co-Researcher:

Name and Degree: Antoney Ferrey, MD

Position/Title and Department: Assistant Professor, Division of Nephrology

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Ferrey will screen and recruit patients in the hospital.

Co-Researcher:

Name and Degree: Omar Darwish, DO

Position/Title and Department: Associate Professor of Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Darwish is Director of the Simulation Center for the Department of Medicine, and Director for point-of-care ultrasound education for Medicine trainees. He will screen and recruit patients in the hospital.

Co-Researcher:

Name and Degree: Isabel Algaze Gonzalez MD

Position/Title and Department: Assistant Professor, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Gonzalez will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Bharath Chakravarthy MD MPH

Position/Title and Department: Vice Chair of Research and Academic Affairs, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Chakravarthy conducts epidemiology studies in the ER population. He will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Claire Chandwani MD

Position/Title and Department: Associate Professor, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Chandwani is Medical Director of the Department of Emergency Medicine. She will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Christopher Fox MD

Position/Title and Department: Professor and Chair, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Fox has extensive experience with ultrasound-focused clinical studies. He will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Robert Katzer MD MBA

Position/Title and Department: Associate Professor, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Katzer is the Associate Director of Emergency Medical Services. He will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Shadi Lahham MD MS

Position/Title and Department: Assistant Professor, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Lahham is Director of Emergency Ultrasound. He will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Mark Langdorf MD MHPE

Position/Title and Department: Professor, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Langdorf will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Eric McCoy MD MPH

Position/Title and Department: Associate Professor, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. McCoy is Director of Emergency Medical Services. He will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Megan Osborn MD MHPE

Position/Title and Department: Associate Professor, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Osborn is the Vice Chair of Education and Associate Dean of Students. She will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Jennifer Roh MD

Position/Title and Department: Assistant Professor, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Roh is Associate Medical Director of Emergency Medicine. She will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Scott Rudkin MD MBA RDMS

Position/Title and Department: Professor, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Rudkin is the Fellowship Director of Clinical Informatics and Chief Medical Information Officer. He will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Sangeeta Sakaria MD MPH MST

Position/Title and Department: Assistant Professor, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Sakaria is the Assistant Residency Program Director for Emergency Medicine. She will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Jeffrey Suchard MD

Position/Title and Department: Professor of Emergency Medicine and Pharmacology

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Suchard is Director of Medical Toxicology and Associate Dean for Basic Science Education. He will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Shannon Toohey MD MAEd

Position/Title and Department: Assistant Professor, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Toohey is the Emergency Medicine Residency Program Director. She will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Warren Wiechmann MD MBA

Position/Title and Department: Associate Professor, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Wiechmann is the Associate Dean of Clinical Science Education &

Educational Technology. He will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Alisa Wray MD

Position/Title and Department: Assistant Professor, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Wray is the Emergency Medicine Associate Program Director. She will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Gabriel Sudario MD

Position/Title and Department: Assistant Professor, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Sudario will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Soheil Saadat MD MPH PhD

Position/Title and Department: Research Specialist, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Saadat will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Miguel Martinez MD

Position/Title and Department: Fellow, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Martinez-Romo is an Emergency Medicine Simulation Fellow who will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Lindsey C. Spiegelman MD

Position/Title and Department: Fellow, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Spiegelman is an Emergency Medicine Clinical Informatics Fellow who will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Jonathan Smart MD

Position/Title and Department: Fellow, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Smart is a Multimedia Design Education Technology Fellow who will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Victor Cisneros MD MPH CPH

Position/Title and Department: Fellow, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Cisneros is an Emergency Medicine Research Fellow in Population Health who will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Jonathan Rowland MD

Position/Title and Department: Fellow, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Rowland is an Emergency Medicine ultrasound fellow who will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Humaira Ali DO

Position/Title and Department: Fellow, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Ali is an Emergency Medicine Simulation Fellow who will screen and recruit

patients in the Emergency Room.

Co-Researcher:

Name and Degree: Amy Briggs MD

Position/Title and Department: Fellow, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Briggs is an Emergency Medicine Wilderness Fellow who will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Andy Nguyen MD

Position/Title and Department: Fellow, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Nguyen is an Emergency Medicine ultrasound fellow who will screen and recruit patients in the Emergency Room.

Co-Researcher:

Name and Degree: Ronald Rivera MD

Position/Title and Department: Fellow, Department of Emergency Medicine

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Rivera is a Multimedia Design Education Technology Fellow who will screen and recruit patients in the Emergency Room.

Research Personnel:

(List Research Personnel only as illustrated per the Research Personnel Heat Map only.)

Name and Degree: Hayden Troutt, BS

Position/Title and Department: Junior Specialist, Division of Nephrology

Team Member will: **[ ]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Hayden Troutt is a clinical research assistant who will review medical records to enter participant data into the RedCAP database.

Research Personnel:

Name and Degree: Alejandro E. Canas, BS

Position/Title and Department: Medical student, UCI School of Medicine

Team Member will: **[X]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Alejandro Canas is a medical student pursuing a Mentored Scholarly Research Project (MSRP) who will screen medical records and conduct data analysis.

SECTION 3: SUBJECT POPULATION(S) (INDIVIDUALS/RECORDS/BIOSPECIMENS)

A. Subjects To Be Enrolled on this UCI protocol (Persons/Records/Biospecimens)

1. Complete the table of subject enrollments below. *Include additional rows for subject category/group, as needed.*
2. If the study involves the use of existing records or biospecimens, specify the maximum number to be reviewed/collected, and the number needed to address the research question.

Category/Group (e.g., adults, controls, parents, children)	**Age Range** (e.g., 7-12, 13–17, adults)	**Maximum Number to be Consented or Reviewed/Collected** (include withdrawals and screen failures)	**Number Expected to Complete the Study *or Needed to Address the Research Question***
Adults – Nonspecific laxative	≥18 years old	30	20
Adults – Sodium polystyrene sulfonate	≥18 years old	30	20
Adults – Patiromer	≥18 years old	30	20
Adults - Zirconium	≥18 years old	30	20
		Total: 120	

B. Overall Study Sample Size

If this is a multi-site study, provide the total number of subjects to be enrolled from all sites.

[X] Not applicable: This study will only take place at UCI, and does not involve other sites.

Total number of subjects across all sites: 120

C. Eligibility Criteria

1. Identify the criteria for inclusion and exclusion.

Inclusion criteria:

- Plasma K > 5.5 mEq/L
- Age ≥ 18 years
- Patient able to provide written informed consent

Exclusion criteria:

- Recent bowel surgery
- Ileus or bowel obstruction
- Pseudohyperkalemia signs and symptoms, such as excessive fist clenching, hemolyzed blood specimen, severe leukocytosis or thrombocytosis
- Pregnancy (studies carry no prospect of benefit to pregnant women who may be assigned to MiraLAX group)
- Active psychiatric disorder
- Possible pseudohyperkalemia
- Diabetic ketoacidosis or hyperkalemia caused by any condition for which a therapy directed against the underlying cause of hyperkalemia would be a better treatment option than treatment with insulin and glucose
- Dialysis session expected within 4 hours after randomization
- History of hypersensitivity to sodium polystyrene sulfonate resin or patiromer
- Concurrent use of sorbitol (due to increased risk of intestinal necrosis when used with sodium polystyrene sulfonate)

2. If eligibility is based on age, gender, pregnancy/childbearing potential, social/ethnic group, or language spoken (e.g., English Speakers only), provide a scientific rationale.

[ ] Not applicable: Subject eligibility is not based on these factors.

Study will be focus on adults due to site not being designated to treat pediatric patients. Children will not be enrolled given lack of sufficient efficacy data in the pediatric population, and there is insufficient data from adults to ensure that children are not exposed to unnecessary risks that may outweigh potential benefits.
The study carries no prospect of benefit to pregnant women who may be assigned to MiraLAX group so pregnant women cannot be included if the research can be conducted by enrolling other subject populations per UC regulations.
The study is open to only English and Spanish-speaking participants as our Subject Symptom Assessment Form is available in these languages.

3. If American Indian or Alaska Native Tribes will be included in the research:
   a. Specify the name of the Tribe and
   b. Specify whether there is Tribal Law that may be applicable to this research and that provides additional protections for subjects (i.e., additional information to be disclosed in the consent process).

[X] Not applicable: American Indian or Alaska Native Tribes are not included in the research.

D. PRE-SCREENING AND DETERMINING ELIGIBILITY WITHOUT INFORMED CONSENT

1. **IMPORTANT NOTES:**
   a. This section is **Not applicable** to research that is funded/supported by the Department of Justice (**DOJ**)
   b. This section addresses pre-screening activities that are performed **without the written informed consent of the prospective subject or legally authorized representative (LAR).** This may be allowed without requesting a waiver of informed consent **IF the following guidelines are utilized**:

[ ] Not applicable: Information and/or biospecimens will not be obtained for the purpose of screening, recruiting, or determining eligibility of prospective subjects. *Skip to Section 4.*

[ ] Study team will obtain information through **oral or written communication** with the prospective subject or LAR (i.e. self-report of medical information; medical records will not be screened).

STOP *Submit recruitment script/s for IRB approval. Be sure to address minimum recruitment requirements and address **the following guidelines**:*

i. *Privacy: The script must address the case where someone other than the potential subject receives the communication. Please be mindful of privacy considerations (i.e., do not disclose any private information – such as a patient diagnosis). Limit phone contact / messages to no more than 5 attempts.*
ii. *Expertise: Study team member/s contacting potential subject must be knowledgeable and able to answer questions related to the screening and the main study.*
iii. *Specific Information: Include a description of the information and/or biospecimens that will be obtained for the purpose of screening, recruiting, or determining eligibility and the reasons for performing the screening tests.*
iv. *Confidentiality: Include a statement that informs the potential subject that if they are not eligible to participate in the study that the identifiable information and / or biospecimens will not be used for research purposes and will be destroyed at the earliest opportunity consistent with conduct of the research.*

[X] Study team will **screen medical records** to determine subject eligibility.

STOP *Complete Appendix T to request a partial waiver of HIPAA Authorization.*

[ ] Study team will **screen medical records** to determine subject eligibility **under IRB approved screening protocol.** Specify HS#: <Type here>

[ ] Study team will **screen non-medical records** (i.e., student records) to which they have access to determine subject eligibility. Specify: <Type here>

[ ] For research accessing student records, check here to confirm that evidence of FERPA[1] compliance has been / will be obtained (and on file) from the local school/district site or the UCI Registrar prior to the initiation of research.

[ ] Study team will **access stored identifiable biospecimens**.

2. For studies that will **screen medical records**, explain how the study team will access the clinical data. *Access to UCI Medical Center medical records for research purposes outside the capacity of the Honest Broker Services, such as access to physician notes, must be obtained from the Health Information Management Services.*

[ ] Not applicable: This study does not involve the screening of medical records.

How Obtained: Indicate all that apply:

[ ] The study team will request specific patient information/data from UCIMC Health Information Management Services.

[X] The study team will review their UCI patients' records and abstract data directly from those records.

[ ] The study team will request specific patient information/data from UCI Health Honest Broker Services. Describe the following:

Cohort selection criteria (e.g., use the available Clinical Terms from the Cohort Discovery Tool such as Demographics: Gender, Diagnoses: Asthma, Procedures: Operations on digestive system): <Type here>

Expected cohort size/patient count: <Type here>

Cohort attributes or data elements (e.g., lab test values, medication, etc.): <Type here>

[ ] The study team will review non-UCI Health records and abstract data directly from those records. Describe the following:

Specify the non-UCI Health records that will be screened: <Type here>

Explain how the study team has access to this clinical data: <Type here>

[ ] Other; explain: <Type here>

3. For studies that will **screen existing biospecimens**:
   a. Indicate the source of the biospecimens and explain how the existing biospecimens will be obtained.
   b. Indicate whether the biospecimens were originally collected for research purposes.

[1] *34 CRF 99: Family Educational Rights and Privacy Act (FERPA) applies to this research.*

[X] Not applicable: This study does not screen existing biospecimens.

How Obtained: Indicate <u>all</u> that apply:
[ ] UCI Health Pathology Biorepository

[ ] Other UCI-Health Entity; specify: <Type here>

[ ] Non-UCI Entity; specify: <Type here>

[ ] Other; explain: <Type here>

Originally collected for research purposes:
[ ] NO – Please explain: <Type here>

[ ] YES – UCI IRB approval granted under IRB protocol number (i.e. HS#): <Type here>

[ ] YES – Non-UCI IRB approval granted. Confirm **<u>one</u>** of the following:

[ ] A copy of the IRB Approval Notice and Consent Form for the original research collection will be submitted with the IRB application (APP). The IRB Approved Consent Form does not preclude the proposed activity.

[ ] A copy of the commercial Vendor Policy or a Letter from the Vendor attesting that the information was collected and will be shared in an appropriate and ethical manner will be submitted with the APP. The vendor's policy does not preclude the proposed activity.

<u>SECTION 4</u>: RECRUITMENT METHODS

Check any of the following methods that will be used to recruit subjects for this study:

[ ] Not applicable: This study involves no direct contact with subjects (i.e., use of existing records, charts, biospecimens).

Specify database or IRB-approved protocol number (HS#), if applicable: <Type here>

[ ] Advertisements, flyers, brochures, email, Facebook, and/or other media.

Specify where recruitment materials will be posted: <Type here>

If subjects will be recruited by mail, e-mail, or phone, specify how their contact information will be obtained: <Type here>

Submit <u>recruitment materials</u> for IRB approval.

[X] The study will be listed on <u>Clinicaltrials.gov</u>. *All Applicable Clinical Trials must be registered.*

[ ] The study will be listed on the <u>Center for Clinical Research (CCR) Find a Trial</u> web page. *This webpage is for UCI School of Medicine departments as well as the clinical research conducted at the Chao Family Comprehensive Cancer Center and the Alpha Stem Cell Center.*

[ ] The study will be listed on the UC Irvine Health Clinical Trials web page.

Submit the UCIMC Standard Research Recruitment Advertisement for IRB approval.

[ ] The UCI Social Sciences Human Subjects Lab/Sona Systems will be used.

Ensure that all applicable consent documents include reference to use SONA.

[X] Referral from colleagues

- Study team will provide colleagues with UCI IRB-approved recruitment materials for distribution to potential subjects (e.g., recruitment flyer, introductory letter);
- An IRB-approved recruitment letter will be sent by the treating physician. The letter will be signed by the treating physician and sent to his/her patients to inform them about how to contact study team members; and/or
- Colleagues obtain permission from interested patient to release contact information to researchers.
- Study team does not have access to patient names and addresses for mailing.
- If colleagues will screen their patients' medical records to determine subject eligibility and approach patients directly about study participation: *Complete Appendix T to request a partial waiver of HIPAA Authorization.*

Submit recruitment materials for IRB approval.

[ ] Study team will contact potential subjects who *have given prior permission to be contacted* for research studies.

Specify when and how these individuals granted permission for future contact: <Type here>

Specify database or IRB-approved protocol number (HS#): <Type here>

[X] Study team members will approach their own patients, students, employees for participation in the study.

[ ] Other Recruitment Methods: <Indicate the recruitment method(s) here>

SECTION 5: INFORMED CONSENT PROCESS

A. Methods of Informed Consent

1. Indicate all applicable informed consent methods for this study. *Submit the consent/assent document(s) with your e-IRB Application (e.g., Study Information Sheet, Recruitment script, Consent Form, etc.). Only IRB approved consent forms (containing the IRB approval footer) may be used to consent human subjects at UCI.*

[X] Signed informed consent will be obtained from subjects. Signed informed consent and/or parental permission will be obtained from subjects, as applicable.

[ ] Requesting a waiver of signed informed consent. Signed consent will not be obtained; consent will be **obtained verbally or via the web**. Informed consent, parental permission and/or child assent will be obtained from subjects, as applicable.

Complete Appendix P.

[ ] Requesting to seek surrogate consent from the subjects' LAR. Surrogate consent may be considered only in research studies relating to the cognitive impairment, lack of capacity or serious or life-threatening disease and conditions of the research subjects.

Complete Appendix E.

[ ] Requesting a waiver of the consent process. Consent will not be obtained. *Skip to Section 5.B.*

Complete Appendix O.

2. Indicate where the consent process will take place.

[X] In a private room
[X] In a waiting room
[X] In an open unit (Emergency Department)
[ ] In a group setting
[ ] The internet
[ ] In public setting
[ ] Over the phone
[ ] Other (specify): <Type here>

3. Specify how the research team will assure that subjects or their LAR have sufficient time to consider whether to participate in the research.

[ ] Subjects or their LAR will be allowed to take home the unsigned consent form for review prior to signing it.

[X] Subjects or their LAR will be allowed 0.5 hours to consider whether to consent.

[ ] Other (specify): <Type here>

4. If children are enrolled in this study, describe the parental permission process and the child assent process.

[X] Not applicable: Children are not enrolled in this study.

<Type here>

5. Some subjects may be vulnerable to coercion or undue influence, such as those who are economically or educationally disadvantaged, have impaired decision-making capacity, or students (undergraduate, graduate, and medical students) and employees of UCI (administrative, clerical, nursing, lab technicians, post-doctoral fellows and house staff, etc.), describe the procedures to ensure the voluntary participation of these individuals.

[ ] Not applicable: Subjects are not vulnerable to coercion or undue influence. Patient will be informed that regardless of their decision to participate in the study, the care they will receive will not be affected by their decision.

[ ] Other (specify): <Type here>

B. Health Insurance Portability and Accountability Act (HIPAA) Authorization

Indicate all applicable HIPAA authorization methods for this study.

[ ] Not applicable: Study does not involve the creation, use, or disclosure of Protected or Personal Health Information (PHI).

[ ] Requesting a Total waiver of HIPAA Authorization. HIPAA authorization will not be obtained at all for the study.

Complete Appendix T.

[X] Requesting a Partial waiver of HIPAA Authorization. HIPAA authorization will not be obtained for screening/recruitment purposes. However, written (signed) HIPAA research authorization is obtained for further access to personal health information.

Complete Appendix T.

[X] Written (signed) HIPAA Research Authorization will be obtained from subjects. Signed authorization, parental authorization, and/or child assent will be obtained from subjects or their LAR, as applicable.

Complete the HIPAA Research Authorization form.

C. Methods of Informed Consent for non-English Speakers

1. Indicate the applicable informed consent method for non-English speakers.

[ ] **Not applicable**: Only individuals who can read and speak English are eligible for this study. *Scientific justification must be provided in Section 3.C.2.*

[X] The English version of the consent form will be translated into appropriate languages for non-English speaking subjects or their LAR once IRB approval is granted. *The translated consent form must be submitted to the IRB for review prior to use with human subjects. Only IRB approved consent forms (containing the IRB approval stamp) may be used to consent human subjects at UCI.*

[ ] Requesting a short form consent process.


Complete Appendix Q.

The short form process will be used for the following occasional and unexpected languages:

[ ] All non-English languages

[ ] All non-English languages except Spanish

[ ] Other languages (specify): <Type here>

2. Explain how non-English speaking subjects or their LAR will be consented in their language and who will be responsible for interpreting and facilitating the informed consent discussion for the non-English speaking subjects.

[ ] At least one member of the study team is fluent in the language that will be used for communication, and that study team member(s) will be available during emergencies.


For all members of the study team responsible for obtaining informed consent from non-English speaking subjects, provide their qualifications to serve in this capacity (i.e. language fluency) in Section 2.

[X] The study team has 24-hour access to a translation service with sufficient medical expertise to discuss the research in this study.

[ ] Other (explain): <Type here>

SECTION 6: RESEARCH METHODOLOGY/STUDY PROCEDURES

A. Study Location

Specify where the research procedures will take place (e.g. UCI Douglas Hospital – Cardiac Care Unit, UCI Main Campus Hewitt Hall, UCI Health – Pavilion II, UCI Family Health Center, Anaheim, Irvine High School).


If research activities will also be conducted at non-UCI locations (e.g., educational institutions, businesses, organizations, etc.), Complete Appendix A. Letters of Permission or other documentation may be required (e.g. Off-site Research Agreements or IRB Authorization Agreements).

UCI Emergency Department, UCI Douglas Hospital, UCI Tower Hospital

B. Study Design

1. Include an explanation of the study design (e.g., randomized placebo-controlled, cross-over, cross-sectional, longitudinal, etc.) and, if appropriate, describe stratification/ randomization/blinding scheme.

Since the patient will only receive one dose in an Emergency Room setting, we are opting for higher medication doses to maximize drug effect for potassium lowering.
Patients are randomized in sequential fashion to one of the treatment groups:

1. Nonspecific laxative (MiraLAX) 17 g packet once
2. SPS 30 g once
3. Patiromer 25.2 g once
4. Zirconium 15 g once

Study medication	**Standard of care? / For research purposes only?**	**Dosage**	**Within FDA recommended dosage?**
Initial therapies for hyperkalemia (e.g., insulin/dextrose, IV fluids/loop diuretic or albuterol)	Standard of care	ED or inpatient physician discretion	Yes
Miralax	Research purposes only	17 g once	No (we are using standard laxative dose)
Kayexalate / SPS	Research purposes only	30 g once	No
Lokelma / Sodium zirconium cyclosilicate	Research purposes only	15 g once	No
Veltassa / Patiromer	Research purposes only	25.2g once	No

2. Provide precise definitions of the study endpoints and criteria for evaluation; if the primary outcomes are derived from several measurements (i.e., composite variables) or if endpoints are based composite variables, then describe precisely how the composite variables are derived.

The primary outcome is change in blood potassium level at 2 hrs and 4 hrs after study drug was administered. Standard therapy will be provided at the discretion of ED or inpatient physician. Final statistical analysis will include adjustment for the use of these therapies (dextrose/insulin, albuterol, diuretics).

C. Research Procedures

1. Provide a detailed chronological description of all research procedures.

1. Hyperkalemia is identified on labs drawn in the ED or hospital. Standard initial therapies for hyperkalemia (e.g., insulin/dextrose, IV fluids/loop diuretic or albuterol) will be initiated per discretion of ED or inpatient physician.
2. Patient is screened to ensure that Inclusion Criteria are met, and that the patient does not meet any Exclusion Criteria.
3. Signed informed consent will be obtained by the Emergency Room or inpatient physician listed on the Consent Form. To ensure that the patient and treating physician are blinded to the study drug, an off-site nephrologist will order the study drug in the Epic medical records system.
4. All study drugs including non-formulary medications (patiromer, zirconium) will be dispensed by the Investigational Drug Services Pharmacy.

5. Follow up blood-draw done at 2 hrs and 4 hrs after medication dose.
6. Research personnel will complete Symptom Assessment form and document Palatability Score with patient at 4 hrs.
7. Subsequent data on length of hospital stay, need for dialysis etc. will be collected by medical chart review.

2. Describe the duration of a subject's participation in the study. If there are sub-studies, include duration of participation in each sub-study.

4-5 hours while in the ED or hospital.

3. List data collection instruments (e.g., measures, questionnaires, interview questions, observational tool, etc.).

Investigator-authored, non-standardized, or un-validated measures must be submitted for review.

Symptom Assessment form
Palatability Score form
Lab results and course of hospital stay from medical records
RedCAP database collection tool

D. UCIMC Supplementary Clinical Services

If a UCIMC clinical unit/department (e.g., phlebotomy for blood draws, pharmacy for dispensing study drug(s), radiation services for X-rays, MRIs, CT scans, and Neurology for lumbar punctures) will perform research-related procedures:

1. List the research procedure (e.g. lumbar puncture, MRI, CT Scan), and
2. Identify the unit/department that will perform the procedure.

[ ] Not applicable: This study does not involve the services of a UCIMC clinical unit/department.

Investigational Drug Services Pharmacy will stock and dispense all study medications including the non-formulary medications (MiraLax, SPS, patiromer, zirconium).

E. Privacy

Privacy is about the subject's ability to control how much others see, touch, or collect information about the subject. Indicate all of the following methods that will be used to assure subject privacy. *Violations of privacy include accessing a subject's private information without consent, asking personal sensitive information in a public setting, being audio recorded or photographed without consent.*

[ ] Research procedures (including recruitment) are conducted in a private room.

[ ] Use of drapes or other barriers for subjects who are required to disrobe.

[X] Only sensitive information directly related to the research is collected about subjects.

[ ] When information is collected from internet sources, the internet site's privacy statement will be reviewed and followed.

Provide a copy of the Data Use Policy to the IRB.

[ ] Other (specify): <Type here>

F. Use of Identifiable Private Information and/or Identifiable Biospecimens as Part of the Main Study

1. For studies that will use **existing identifiable biospecimens** as part of the **main study** (not for determining eligibility):
   a. Indicate the source of the biospecimens and explain how the existing biospecimens will be obtained.
   b. Indicate whether the biospecimens were originally collected for research purposes.

[X] **Not applicable**: This study does not use existing biological specimens as part of the main study.

How Obtained: Indicate <u>all</u> that apply:

[ ] UCI Health Pathology Biorepository

[ ] Other UCI-Health Entity; specify: <Type here>

[ ] Non-UCI Entity; specify: <Type here>

[ ] Other; explain: <Type here>

Originally collected for research purposes:

[ ] NO – Please explain: <Type here>

[ ] YES – UCI IRB approval granted under IRB protocol number (i.e. HS#): <Type here>

[ ] YES – Non-UCI IRB approval granted. Confirm **<u>one</u>** of the following:

[ ] A copy of the IRB Approval Notice and Consent Form for the original research collection will be submitted with the IRB application (APP). The IRB Approved Consent Form does not preclude the proposed activity.

[ ] A copy of the commercial Vendor Policy or a Letter from the Vendor attesting that the information was collected and will be shared in an appropriate and ethical manner will be submitted with the APP. The vendor's policy does not preclude the proposed activity.

2. For studies that will **use identifiable clinical data** as part of the **main study** (not for determining eligibility), indicate the source and how the study team will access the medical records. *Access to UCI Medical Center medical records for research purposes outside the capacity of the Honest Broker Services, such as access to physician notes, must be obtained from the Health Information Management Services.*

For investigator initiated/authored studies only, submit a data abstraction sheet that includes a complete list of data elements/information that will be collected from (existing) records or submit the case report form (CRF; eCRF).

[ ] Not applicable: This study does not involve the use of identifiable clinical data as part of the main study. *Skip to Section 6.G.*

How Obtained: Indicate all that apply:

[ ] The study team will request specific patient information/data from UCIMC Health Information Management Services.

[X] The study team will access their UCI patients' records and abstract data directly from those records.

[ ] The study team will request specific patient information/data from UCI Health Honest Broker Services. Describe the following:

Cohort selection criteria (e.g., use the available Clinical Terms from the Cohort Discovery Tool such as Demographics: Gender, Diagnoses: Asthma, Procedures: Operations on digestive system): <Type here>

Expected cohort size/patient count: <Type here>

Cohort attributes or data elements (e.g., lab test values, medication, etc.): <Type here>

[ ] The study team will request non-UCI Health records and abstract data directly from those records. Describe the following:

Specify the non-UCI Health records that will be screened: <Type here>

Explain how the study team has access to this clinical data: <Type here>

[ ] Other; explain: <Type here>

3. For studies that involve use of existing (i.e. on the shelf; currently available) clinical data, specify the time frame of the clinical data to be accessed (e.g. records from January 2002 to initial IRB approval).

N/A

G. Collection of Photographs, or Audio/Video Recording

1. Describe all procedures involving the use and/or collection of photographs, or audio/video recording.

[X] Not applicable: This study does not involve photographs or audio/video recording. *Skip to Section 6.H.*

<Type here>

2. Specify if photographs or audio/video recording will include subject identifiable information (e.g., name, facial image). If so, indicate which identifiers will be collected.

<Type here>

3. Explain whether the photographs or audio/video recording will be included in subsequent presentations and/or publications and, if so, whether subject identifiers will be included.

<Type here>

H. Sharing Results with Subjects

1. Describe whether individual results (results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subject or others (e.g., the subject's primary care physician). *Only tests ordered by a physician and conducted in a CLIA certified lab may be shared.*
2. Explain what information will be shared and how the results will be shared.

[X] Not applicable: Individual results will not be shared with subjects.

<Type here>

3. Describe whether overall study results will be shared with subjects.
4. Explain how results will be shared.

[X] Not applicable: Final study results will not be shared with subjects.

[ ] The overall study results will be listed on Clinicaltrials.gov. *All Applicable Clinical Trials must be registered.*

[ ] Other: <Type here>

I. Statistical Considerations *(This section is required for Investigator-Authored Research)*

1. Statistical Analysis Plan: Describe the statistical method(s) for the stated specific aims and hypotheses.

The Biostatistics, Epidemiology and Research Design (BERD) Unit under the Institute for Clinical and Translational Science (ICTS) can assist in developing power and sample size calculation. Visit: http://www.icts.uci.edu/services/berd%20request.php *for a consultation.*

Your analysis plans should match the stated study specific aims and hypotheses in Section 1.

For cancer related research: The Chao Family Comprehensive Cancer Center's Biostatistics Shared Resource (BSR) assists investigators with the design of new studies, power and sample

size calculations, and data analyses. To request BSR support, visit: https://www.cancer.uci.edu/biostatistics/consultation.asp"

[ ] Not applicable: A statistical analysis plan is not appropriate for this qualitative study design. Plan for assessing study results: <Type here>
Skip to Section 7.

We will calculate absolute change in blood potassium level at 2 hr and 4 hr after medication dose.
Multivariate adjustment will be done for comorbid conditions and other relevant clinical factors:

- Serum creatinine and eGFR
- Acute kidney injury or CKD or chronic dialysis status
- Diabetes mellitus
- CHF
- RAAS inhibitor medication (ACEi or ARB)
- Metabolic acidosis

Use of other interventions (insulin/dextrose; diuretics; bicarbonate; calcium gluconate; albuterol)

2. Describe the primary statistical method(s) that will be used to analyze the primary outcome(s) or endpoints.

One-way analysis of variance (*ANOVA*) to compare mean change in blood potassium between the 4 groups, P set at 0.05.

3. Describe the secondary statistical method(s) that will be used to analyze the secondary outcome(s) or endpoints.

A Cox model with multivariate adjustment will be done for comorbid conditions and other relevant clinical factors listed above.

Safety and tolerability will be assessed using a Kruskal-Wallis test to globally test for a negative trend across all five study treatments and, if significant (two-sided $p<0.05$), then using a two-sided Fisher Exact test compare each active dose vs. nonspecific laxative control.

4. If appropriate describe secondary or post hoc analyses of primary outcome(s) or other exploratory analysis.

N/A

5. Sample Size Determination**:** Explain how the overall target sample size was determined (e.g., power analysis; precision estimation), providing justification of the effect size for the primary outcome based on preliminary data, current knowledge/literature and/or cost consideration; if appropriate, provide sample size justification for secondary outcomes. Power analysis should (at least) match the primary outcome/endpoint.

Assuming a difference in blood potassium level of 1 mEq/L between the nonspecific laxative and the zirconium group, and within-group standard deviation 0.5 mEq/L
With alpha error set at 0.05
And power set at 0.9
We need at least 6 subjects per group to detect a significant difference between the groups. We are aiming for 20 patients per group for final analysis to ensure adequate numbers for comparison. The SlicerDicer tool within Epic estimated 1,055 cases of hyperkalemia in the ED in year 2018,

thus our target for a final cohort size of 80 is reasonable.

SECTION 7: RISK ASSESSMENT AND POSSIBLE BENEFITS

A. Risk Assessment

1. Indicate the appropriate level of review of this study, based upon your risk assessment.

[ ] This study involves greater than minimal risk to subjects and requires Full Committee review. *Skip to Section 7.B.*

[X] This study involves no more than minimal risk and qualifies as **Expedited research**.

2. If this study involves no more than minimal risk, provide justification for the level of review and for all applicable Expedited Categories you have chosen.

Expedited Category 1a: This proposal is a clinical study of drugs where an IND is not required. The potassium exchange resins are already FDA approved for use in the chronic management of hyperkalemia, but data is lacking on their relative efficacy in the acute hyperkalemia setting.

B. Risks and Discomforts

1. Describe and assess any reasonably foreseeable risks and discomforts — physical, psychological, social, legal or other. Include an assessment of their expected frequency (e.g., common – 65%, less common – 40%, unlikely – 5%, rare - <1%) and the seriousness (mild, moderate, severe). *A bullet point list is recommended. If this study will involve the collection of identifiable private information, even temporarily, for which the disclosure of the data outside of the research could reasonably place the subjects at risk, include the risk of a potential breach of confidentiality.*

As listed in the UCI consent form.

2. Discuss what steps have been taken and/or will be taken to prevent and minimize any risks/ potential discomforts to subjects. *Examples include: designing the study to make use of procedures involving less risk when appropriate; minimizing study procedures by taking advantage of clinical procedures conducted on the subjects; mitigating risks by planning special monitoring or conducting supportive inventions for the study; implement security provisions to protect confidential information.*

Potential side effects of potassium exchange resins: This is not a blinded study; if a patient reports that they had significant side effects previously with a potassium binder, they can choose to drop out of the study.

Venipuncture: Blood draws will be performed by trained UCI medical center personnel.

Confidentiality: We will protect subject confidentiality by maintaining data in a password-protected secure RedCAP database.

C. Potential Benefits

1. Describe the potential benefits subjects may expect to receive from participation in this study. *Compensation is not a benefit; do not include it in this section.*

[ ] There is no direct benefit anticipated for the subjects.

Patients treated with zirconium may potentially experience more rapid normalization of blood potassium levels.

2. Specify the expected potential societal/scientific benefit(s) of this study.

The study would inform medical practitioners who deal with acute hyperkalemia treatment, on the most effective choice of potassium exchange resin with least side effects. This has potential significant impact on decreasing duration of ED or hospital stay, improving patient satisfaction and well-being, and saving healthcare dollars.

SECTION 8: ALTERNATIVES TO PARTICIPATION

Describe the alternatives to participation in the study available to prospective subjects. Include routine (standard of care) options as well as other experimental options, as applicable.

[ ] No alternatives exist. The only alternative to study participation is not to participate in the study.

[X] There are routine standard of care alternatives available; specify: Patients will receive standard of care hyperkalemia management regardless of their participation in the study.

[ ] There are other alternatives to study participation; specify: <Type here>

SECTION 9: SUBJECT COSTS

1. Indicate below if subjects or their insurers will be charged for study procedures. Identify and describe those costs.

[ ] Not applicable: This study involves no interaction/intervention with research subjects. *Skip to Section 10.*

[ ] This study involves interaction/intervention with research subjects; however there are no costs to subjects/insurers.

[X] This study involves interaction/intervention with research subjects, and there are costs to subjects/insurers: All study medications will be purchased via the PI's discretionary research funds (from Division of Nephrology, Department of Medicine). Lab monitoring at 2 hr and 4 hr fall within standard of care for monitoring of electrolyte derangements in the ED or hospital, which will be charged to subjects/insurers.

2. If subjects or their insurers will be responsible for study-related costs, explain why it is appropriate to charge those costs to the subjects or their insurers. Provide supporting documentation as applicable (e.g., study procedures include routine (standard of care) procedures; FDA IDE/HDE/IND letter that supports billing to subjects).

[ ] Not applicable: The study involves no costs to subjects for study participation.

[X] Study related costs will be billed to subjects or their insurers for the following reasons: Standard of care costs will be billed to insurers/subjects such as labs drawn at the 2 and 4 hours time-points to monitor electrolyte disturbances.

SECTION 10: SUBJECT COMPENSATION AND REIMBURSEMENT

1. If subjects will be compensated for their participation, explain the method/terms of payment (e.g., money; check; extra credit; gift certificate).

[ ] Not applicable: This study involves no interaction/intervention with research subjects. *Skip to Section 11.*

[X] No compensation will be provided to subjects.

[ ] Compensation will be provided to subjects in the form of cash/gift certificate.

[ ] Compensation will be provided to subjects in the form of a check issued to the subjects through the UCI Accounting Office. The subject's name, address, and social security number, will be released to the UCI Accounting Office for the purpose of payment and for tax reporting to the Internal Revenue Service (IRS).

[X] Other: Each member of the Data & Safety Monitoring Board will be given a $50 gift card for completing each quarterly review.

2. Specify the schedule and amounts of compensation (e.g., at end of study; after each session/visit) including the total amount subjects can receive for completing the study. *Compensation should be offered on a prorated basis when the research involves multiple visits.*

   For compensation ≥ $600, subject names and social security numbers must be collected. This information must be reported to UCI Accounting for tax-reporting purposes.

[X] Not applicable: This study involves no compensation to subjects.

Subjects will be compensated with the following schedule and amounts: <Type here>

3. Specify whether subjects will be reimbursed for out-of pocket expenses. If so, describe any requirements for reimbursement (e.g., receipt).

[X] Not applicable: This study involves no reimbursement to subjects.

Subjects will be reimbursed; specify: <Type here>

SECTION 11: CONFIDENTIALITY OF RESEARCH BIOSPECIMENS/DATA

A. Information and/or Biospecimens Storage

1. Indicate how information and/or biospecimens will be stored and secured. Check all that apply:

[X] Information will be maintained electronically. Information will be password protected and maintained in an encrypted format. *Researchers may access UCI-contracted data sharing and storage tools through UCI OIT.*

[ ] Information will be maintained in hard copy. Information will be stored in a locked area that is not accessible to non-study team members.

[ ] Biospecimens will be stored in a locked lab/refrigerator/freezer that is not accessible to non-study team members.

2. List the location(s) where the data and/or biospecimens will be stored**.**

Secure RedCAP database. Only de-identified data will be exported for final analysis.

3. Indicate all subject identifiers that may be retained with the information and/or biospecimens collected for the research study. *If any study-related data will be derived from a medical record, added to a medical record, created or collected as part of health care, or used to make health care decisions the HIPAA policy applies. The subject's HIPAA Research Authorization is required or a waiver of HIPAA Research Authorization must be requested by completing Appendix T.*

[ ] This study does not involve the collection of subject identifiers.

Check all the following identifiers will be used, created, collected, disclosed as part of the research:

[X] Names	**[ ]** Social Security Numbers	**[ ]** Device identifiers/Serial numbers
[X] Dates*	**[X]** Medical record numbers	**[ ]** Web URLs
[ ] Postal address	**[ ]** Health plan numbers	**[ ]** IP address numbers
[ ] Phone numbers	**[ ]** Account numbers	**[ ]** Biometric identifiers
[ ] Fax numbers	**[ ]** License/Certificate numbers	**[ ]** Facial Photos/Images
[ ] Email address	**[ ]** Vehicle id numbers	**[ ]** Any other unique identifier

[ ] Other (Specify all): <Type here>

* *birth date, treatment/hospitalization dates*

4. Indicate if a code will be used to link subject identifiers with the information and/or biospecimens.

[ ] Not applicable: No subject identifiers will be collected.

[ ] A code will be used (i.e. information and/or biospecimens will be coded). Subject **identifiers** will be **kept separately** from the information and/or biospecimens. The code key will be destroyed at the earliest opportunity, consistent with the conduct of this research.

[X] A code will not be used. Subject **identifiers** will be **kept directly** with the information/biospecimens.

5. If **subject identifiable data** will be transported or maintained on **portable devices**, explain why it is necessary use these devices. *Only the "minimum data necessary" should be stored on portable devices as these devices are particularly susceptible to loss or theft. If there is a necessity to use a portable device for the initial collection of identifiable private information, the research files must be encrypted, and subject identifiers transferred to a secure system as soon as possible.*

[X] Not applicable: Research data will not be transported or maintained on portable devices.

[ ] Research data will need to be maintained on the following portable device(s) for the following reason(s): <Type here>

B. Information and/or Biospecimens Access

1. Specify who will have **access to subject identifiable information and/or identifiable biospecimens** as part of this study. Check all that apply.

[ ] Not applicable: No subject identifiers will be collected.

[X] Authorized UCI personnel such as the research team and appropriate institutional officials, the study sponsor or the sponsor's agents (if applicable), and regulatory entities such as the Food and Drug Administration (FDA), the Office of Human Research Protections (OHRP), and the National Institutes of Health (NIH).

[ ] Other: <Type here>

2. Specify whether subject identifiers be disclosed in presentations and/or publications.

[ ] Not applicable: No subject identifiers will be collected.

[X] Subject identifiers will **not** be disclosed.

[ ] Subject identifiers will be disclosed. Text regarding the disclosure will be included in the consent document and specific permission to disclose will be discussed with subjects.

3. Specify whether **information and/or biospecimens be shared** with other researchers **outside of the study team** (i.e., UCI / non-UCI researchers) for secondary research purposes. *When accessing/transferring data from/to a non-profit, please contact Grace J. Park at parkgj@uci.edu. When accessing/transferring data from/to a for-profit, please contact the Industry Contract Officer at UCI Beall Applied Innovation assigned to your department.*

[X] Not applicable: information and/or biospecimens will not be shared.

[ ] Identifiable information and/or identifiable biospecimens may be shared. Text regarding the information/specimens sharing will be included in the consent document and specific permission to share information will be discussed with subjects.

Check one of the following:

[ ] A biorepository will be established and manage by the UCI study team. ***Submit Appendix M.***

[ ] Subject identifiers will be retained in an established non-UCI biorepository (i.e. not managed by the UCI study team). The non-UCI biorepository has a current IRB approval on file.

Specify the non-UCI biorepository: <Type here>

[ ] De-identified information and/or de-identified biospecimens may be shared (i.e. research participants cannot be identified by other researchers). Text regarding the information/biospecimens sharing will be included in the consent document, as applicable.

Check one of the following:

[ ] No subject identifiers will be retained by the study team beyond initial collection (i.e. information/biospecimens cannot be linked to an individual and a key code does not exist). Requests for de-identified information and/or de-identified biospecimens will be managed by the UCI study team.

[ ] Subject identifiers will be retained by the study team beyond initial collection (i.e. information/biospecimens can be linked to an individual and/or a key code exists). A biorepository will be established and managed by the UCI study team. ***Submit Appendix M.***

[ ] Subject identifiers will be retained by the study team beyond initial collection (i.e. information/biospecimens can be linked to an individual and/or a key code exists). De-identified information/biospecimens will be retained and managed in an established non-UCI biorepository (i.e. not managed by the UCI study team). The study team will remove any information that could potentially allow for the re-identification of participants prior to sending the information/biospecimens to the non-UCI biorepository. Specify the non-UCI biorepository: <Type here>

[ ] Other: <Type here>

C. Research Information and/or Biospecimens Retention

1. Indicate how long research information and/or biospecimens will be retained.
2. If more than one option applies, indicate accordingly.
3. If research involves Protected Health Information (PHI): Investigators must destroy PHI at the earliest opportunity, consistent with the conduct of this study, unless there is an appropriate justification for retaining the identifiers or as required by law. Otherwise, identifiable data is to be retained as noted below.

UPDATED! In accordance with UCOP policy, information/biospecimens will be retained for 10 years after the end of the calendar year in which the research is completed, unless otherwise specified in the award agreement. Choose the longest retention period applicable to the study:

[X] There is no contract or award associated with this research. Information/biospecimens will be retained for 10 years after the end of the calendar year in which the research is completed.

[ ] The contract or award associated with this research requires that information/biospecimens be retained for the following period; specify time frame: <Type here>.

[ ] The study is conducted under an IND or an IDE investigation, information/biospecimens will be retained for two years after an approved marketing application. If approval is not received, the information/biospecimens will be kept for 2 years after the investigation is discontinued and the FDA is notified per FDA sponsor requirements.

[ ] This research includes the potential for future **secondary research using**

information/biospecimens which will be stored and maintained indefinitely.

D. Audio/Video Recordings & Photographs

1. If subject identifiable audio/video recordings will be collected, specify the timeframe for the transcription and/or de-identification.
2. If subject identifiable photographs will be collected, specify the timeframe for de-identification.

UPDATED!

[X] Not applicable: Identifiable audio/video recordings and/or photographs will not be collected.

Transcription:

[ ] Audio/video recordings transcribed; specify time frame: <Type here>

[ ] Audio/video recordings will NOT be transcribed; specify why: <Type here>

De-Identification:

[ ] Subject identifiable audio/video recordings & photographs will be de-identified;

- specify time frame: <Type here>
- specify how (ex. real name replace with pseudonym during transcription; blurred facial features): <Type here>

[ ] Subject identifiable audio/video recordings & photographs will NOT be de-identified; specify why: <Type here>

E. Certificate of Confidentiality

1. Indicate whether a Certificate of Confidentiality (CoC) has been or will be requested.

[X] Not applicable: No CoC has been requested for this study.

[ ] This is a non-NIH funded/supported study. Choose one of the following:

[ ] A CoC will be requested for this study. *The CoC application must be submitted to the IRB staff for review after IRB approval.*

[ ] A CoC has been obtained for this study. *Provide a copy of the CoC Approval Letter.* The expiration date of this CoC is: <Type here>

[ ] This is an NIH funded/supported study and a CoC will be automatically issued for studies that involve identifiable, private, and sensitive information.

2. Explain in what situations the UCI study team will disclose identifiable private information protected by a CoC.

<Type here>