

Study Title: Bone in CKD Alkali Response Pilot Trial
(BICARb Pilot Trial)

NCT#: **NCT05918029**

ID: **2023-14826**

IRB Approval Date: **04/26/2025**

Bone in CKD Alkali Response Pilot Trial (BICARb Pilot Trial)

National Clinical Trial (NCT) Number: 05918029

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Participating / Recruiting Centers

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Participating / Supporting Centers

Columbia University Irving Medical Center
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Grant Number: R01DK131811

Protocol Version Number: v.8.0

PROTOCOL AMENDMENTS

VERSION	PROTOCOL VERSION DATE	SUMMARY OF CHANGES
2.0	12/15/2022	N/A
2.0 (WITH CHANGES)	1/26/2023	Updated text to add some FDA recommendations: (a) contraceptive requirements for any female (adult or pediatric) of childbearing potential during the study; (b) Baseline ECG for all study subjects to exclude those with any ECG abnormalities; (c) ECG is repeated at any time during the study when a participant experiences hyperkalemia > 6.5 mEq/L. Protocol sections affected by one or more of these changes: • Protocol summary table 1: Pediatric/Adult Inclusion criteria • Section #4. Inclusion/Exclusion criteria • Section #9: Procedures Involved and Figure 3 for schedule of procedures • Risk to Subjects • Withdrawal of subjects • Trial safety and monitoring plan
3.0	5/1/2023	Updated protocol version (First page and footer). Adding a Co-Investigator from Albert Einstein School of Medicine. Updating text throughout the entire document: • BRANY IRB was replaced by Columbia University IRB as the single IRB (sIRB). • Modification of definition for hyperkalemia: lowered the threshold for hyperkalemia from > 6.5 mEq/L to ≥ 6.0 mEq/L. Adding Protocol Amendments page. Protocol synopsis: Updated protocol summary table (subjects, inclusion criteria). Adding project summary/abstract sections page. Section #2: Updated AIMS. Short text version replaced by a fully detail text as described in the Grant Submission to provide more information to CU sIRB. Section #3: Reference moved to the end (before Appendix section). Section #4: • Renamed as Subject selection and withdrawal. Section #7 (Number of Subjects) moved to be added as a part of Section #4 (4.1). • Inclusion/Exclusion criteria table 3. • Updated text to add PTH, Phosphorus and Vitamin D25 to the screening criteria. • Children and adult cut-off age modified to be in accordance with the legal adult definition in the US. • Section 4.3. Updated text to add “capable” ...informed assent will also be obtained from the capable pediatric participants. Section #5: Setting. • Updated text to state the participating centers roles and provide more information about Lead Institution/Coordinating Center and study sites roles to CU sIRB. • Potential Participant population: Text edited to remove redundant information. Prior Section #6- Resources: Updated to remove redundant text in The University of Utah paragraph. Entire section moved to the end as Appendix A: Resources. Section #7- Recruitment Methods: • Updated to removed Endocrinology and some redundant information from University of Pittsburgh - Children’s Hospital of Pittsburgh (CHP) paragraph.

		• Payment to subjects updated. Section #9- Procedures involved. • Updated text to add fully description of all study procedures to provide this information to CU sIRB. • Medication adherence replaced by study drug adherence to differentiate clinical medications log from study drugs. Section #10- Study design and study visits added. • Updated text to specify the precise timepoints when study visits will occur as recommended by the FDA previously. • Addition of an in-person screening visit. • Updated text to add information about management of medications and supplements used to treat CKD-mineral and bone disease, and a paragraph to state the Instructions on how to take the study drug. • Updated text to specify the stratified randomization. • Updated text to remove calcium and creatinine as a part of the safety labs. • Table 5 renamed as Figure 3 has been updated. Section #11- Specimen banking & genetic testing: Updated text to state the time point of occurrence and the data and specimens' storage timeframe. Section #13-Protecting the privacy of subjects: Updated text to state participants will be provided an appointment for an in-person screening visit. Section #14- Ensuring the safety of subjects. Updated text to add: Reporting to DSMB. Section #15- Risks to subjects. • Updated text to lower the threshold for hyperkalemia from > 6.5 mEq/L to ≥ 6.0 mEq/L. • Updated text to take out total calcium and serum creatinine as criteria to remove participants from the study. This also affect section about withdrawal of subjects. • Radiation: Updated text to state "We added 20 μSv to cover up to two repeat scans per visit in the event of movement". • Updated text to add Pregnancy and breastfeeding risk. Section #17- Prior approvals. Updated text to add Collaborative agreements plan. Section #18 - Consent process and documentation. Updated text to add information about the in-person screening visit. Section #19 - Research Pharmacy: Updated text to change the Generic Potassium Citrate provider and address. Section #21- Trial safety and monitoring plan. • Updated text to provide a plan by each visit. • Updated text to lower the threshold for hyperkalemia from > 6.5 mEq/L to ≥ 6.0 mEq/L. • Updated text to add REDCap data collection information. • Updated text to add Study Stoppage Criteria • Updated text to add a fully description of the Study monitoring activities.
4.0	7/10/2023	Section #7. Recruitment methods. • Text edited to clarify it is A HIPAA waiver will be obtained for preparatory to research activity. • Text edited to add information about PRE-CONSENT PHONE CALL • Payment to subjects: Text edited to fix a typographical error and add "or equivalent". Section #18. Consent process and documentation. • Text edited to remove e-consent via REDCap and to add "written assent" for clarification.

5.0	10/27/2023	1. Updated text to address FDA advice/information request to (i) include serum alkaline phosphatase with the baseline laboratory assessment, and checking serum 25-hydroxy-vitamin D, intact PTH, phosphate, and alkaline phosphatase levels at the 3- and 6-month study visits to ensure that levels remain stable compared to baseline. (ii) putting back into the protocol, serum calcium and creatinine levels as Safety labs. These recommendations affect the following sections. Protocol synopsis (Table 1), and Section #4.2-Inclusion and exclusion criteria. Table 3. • Updated text to add alkaline phosphatase to inclusion criterion #4. • Fixing numeration of "Pediatric and Adult Exclusion". #10 was assigned to two different exclusion criteria. Total exclusion criteria changed from 18 to 19. Section #9- Procedures involved. Research blood sampling. • Updated text to add Blood for Monitoring labs. Section #10- Study design and study visits. • Updated text to add creatinine and calcium as Safety labs. • Updated text to add measurement of alkaline phosphatase at baseline, and serum 25-hydroxy-vitamin D, intact PTH, phosphate, and alkaline phosphatase levels at the 3- and 6-month study visits. • Figure 3 updated to incorporate the Monitoring labs. Section #14- Ensuring the safety of subjects/ Report to DSMB, and Section #21- Trial Safety and Monitoring plan/ Study Stoppage Criteria • Updated text to remove redundant language about definition of the Study stoppage criteria. Section #15- Risk to subjects and Section #21- Trial Safety and Monitoring plan. • Safety monitoring for hyperkalemia and alkalosis and Visit 2-3 (Run-in Phase). Updating text to add creatinine and calcium as Safety labs. Section #15- Risks to subjects- Other potential side effects, and Withdrawal of subjects (Phase 1) • Updated text to add calcium levels <7.5 mg/dL and serum creatine translating to eGFR <20 ml/min per 1.73m² as parameters to consider to subject-level removal criteria. 2. To separate the medication reconciliation form from other study questionnaires. • Section #10 Study design and study visits. Figure 3 updated. 3. Section #17- Sharing of results with subjects and other sites. • Table of agreements between Columbia and other Institutions. Updated text to change the type of agreement with University of Pittsburgh.
6.0	2/21/2024	1. Dr. Michal L. Melamed changed her affiliation from Albert Einstein College of Medicine (AECOM) to New York University/NYU Langone Health. Dr. Melamed will remain involved as a supporting investigator. Dr. Matthew Abramowitz, MD, MS has been assigned as Co-Investigator and adult consultant at AECOM. These changes affect the following protocol sections: Page 1. Study Co-Investigators and Participating / Supporting Centers. • Text edited to add Mathew Abramowitz, MD, MS as Co-Investigator. • Text edited to add NYU Langone Health as Participating/Supporting Centers. • Text edited to update Protocol version number. Section #5: Settings • Text edited to add NY Langone Health as site engaged in the research not involved in enrolling participants. Section #7: Recruitment methods at Albert Einstein College of Medicine • Text edited to remove Dr. Melamed and add Dr. Abramowitz.

		Appendix A: RESOURCES. - Text edited to removed Dr. Melamed and add Dr. Abramowitz in section. Albert Einstein College of Medicine/ Montefiore Medical Center. Department of Medicine. Division of Nephrology; and Individual Investigator resources. - Text edited to add NYU Langone Health. 2. Minor changes to existing E/I criteria. Protocol synopsis (table 1) - Pediatric and adult Inclusion criteria #4 edited to set up a cut-off values for PTH, alkaline phosphatase and phosphorous. Section #4.2: Inclusion and Exclusion criteria. Table 3. - Pediatric and adult Inclusion criterion #4 edited to set up a cut-off values for PTH, alkaline phosphatase and phosphorous. - Pediatric and adult Exclusion criterion #13. Text edited to add "or an unstable dose of" glucocorticoids. 3. Section #9. Procedures involved. Research blood sampling. For monitoring labs. - Text edited to add phosphate. 4. Section #9. Procedures involved. Randomization and Treatment. - Text edited to add "and Investigational Drug Services at the University of Pittsburgh Medical Center (UPMC) Children's Hospital of Pittsburgh." 5. Section#17: Sharing of results with subjects and other sites. Agreement table. Coverage column: Replacing the word "material" for data. 6. Section #19- Research pharmacy. - Text edited to separate the Montefiore Medical Center Research Pharmacy from Investigational Drug Services at UMPC Children's Hospital of Pittsburgh. - Text edited to add "At end of study, CUIMC research team will perform pill count for adults' participants who come to complete the last in-person visit. CUIMC will return any unused drug to MMC for destruction." - Text edited to add information about Investigational Drug Services at UMPC Children's Hospital of Pittsburgh. - Text edited to add description of Randomization at both study sites.
7.0	7/10/2024	1. Serum potassium values were adjusted from 6.6 to 5.9 mEq/L in the following sections: - Section#10. Study Design and Study Visits. - Phase 1 of study (Visits 2, 2- week duration; Visit 3 Run-in phase, 4-6- week duration). - Phase 2 of study (Visits 4 at 3 month and 5 at 6-month after starting the study drug, Randomized Clinical Trial; 6 months duration). - Figure 3: Schedule of procedures/visits for across the duration of the investigation. - Section #15. Risks to subjects. Safety monitoring for hyperkalemia and alkalosis. - Section #21. Trial Safety and Monitoring plan. Visit 2-3 (Run-in Phase) 2. Personnel changes: Appendix A. Albert Einstein College of Medicine/ Montefiore Medical Center Individual Investigator Resources. Text edited to replace Ms. Lisandra Villalba with Mr. Jordan Nacimba. 3. Protocol version number and footer were updated.

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8.0	12/3/2024	- Change of the Columbia PI from Dr. Nickolas to Dr. Mishaela Rubin. - Added Dr. Rubin as ColInvestigator on page 1 - Changes from Dr. Nickolas to Dr. Rubin in the following sections: Section 5 page 17, 18; Section 21, page 47-48, 50 - Added name of Dr. Rubin and coinvestigator Dr. Abramowitz to Section 18 page 43 - Add Einstein at the site for drop-off for 24 hour urine study procedures related to Visits 2 and 5. Section 10, Page 6, Figure 3 updated to show 24/12 hour urine process and shipping to Utah to be done at Einstein for V2 and V5 - Protocol Synopsis Table 1 and Section 4.2 Change eGFR inclusion criteria from > 30 to > or = 30 to be inclusive of all participants with CKD stage 3b (which is inclusive of eGFR 30) - Section 10, page 25. Provided protocol for repeating screening labs in consented patients if they do not meet eligibility on initial screening labs. - Extra spaces were deleted and header/footer was updated to 12/3/2024 - Visit 2 and Visit 5 will occur at Einstein. Only bone imaging to be performed at CUIMC. Table 3 updated Pill count removed from section 19 - Section 10: Changed the time interval allowed between screening to visit 2
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PROTOCOL SYNOPSIS

Table 1. Protocol Summary Table

Title	Bone in CKD Alkali Response Pilot Trial (BICARb Pilot Trial)	
Objectives	The purpose of this study is to determine the effects of potassium citrate on bone quality and strength in patients with chronic kidney disease. Our specific aims are: 1) To evaluate effects of potassium citrate treatment on bone quality and strength 2) To evaluate mechanism(s) underlying the effects of potassium citrate on skeletal health	
Sites	Albert Einstein College of Medicine/ Montefiore Medical Center / Children's Hospital at Montefiore Columbia University Irving Medical Center Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center University of Utah Health	
Number of Participants	88 Adults (older than or equal to 18 years) 15 Children (5 years to 17 years old)	
Study Duration	Phase 1 (Run-in phase) 4-6 weeks duration: Phase 2 (Randomized Clinical Trial Phase): 6 months	
Study Drug (Dosing)	Potassium Citrate extended-release tablets 30 mEq twice daily for adults (1 mEq/kg/day divided into two doses for children to a maximum dose of 30 mEq twice daily) Or Potassium citrate and citric acid for oral solution 1 mEq/kg/day divided into two doses to a maximum dose of 30 mEq twice daily (for children who cannot take pills) Or Placebo	
Study Design	Run-in period followed by placebo-controlled randomized clinical trial.	
Inclusion Criteria	Pediatric Inclusion	Adult Inclusion
	1) Children 5-17 years old	1) Adults ≥ 18 years old
	2) Estimated eGFR ≥ 30 and < 90 ml/min/1.73m ² by CKiD U25 (For Pediatric participants) equations	2) Estimated eGFR ≥ 30 and < 90 ml/min/1.73m ² by the new CKD-Epi without race (For Adults)
	3) Females of child-bearing potential must have had a menstrual period in the last month	3) Pre-menopausal women of childbearing age must have had a menstrual period in the last month
	4) Levels of PTH and, alkaline phosphatase within 2x normal range and phosphorus within the normal range for age (per local laboratory reference assay)	4) Levels of PTH and, alkaline phosphatase within 2x normal range and phosphorus up to 5.0 mg/dL (per local laboratory reference assay)
	5) Levels of 25-hydroxy Vitamin D ≥ 20 ng/mL	5) Levels of 25-hydroxy Vitamin D ≥ 20 ng/mL
	6) Females of childbearing potential must be willing to use one form of effective contraception over the course of the study	6) Women of childbearing potential must be willing to use one form of effective contraception over the course of the study
	7) Proficiency in English or Spanish	7) Proficiency in English or Spanish
	8) For participants < 18 years, the participant and/or parent/guardian capable of providing informed consent and assent (assessed by the provider)	

PROJECT SUMMARY/ABSTRACT SECTION

Chronic kidney disease (CKD) is a state of impaired bone quality and strength. Renal osteodystrophy (ROD), a global disorder of bone strength, is present in the vast majority of CKD patients. Fracture rates are 2- to 14-fold greater in patients with than without CKD and increase in parallel with CKD severity. CKD in children significantly impairs bone architecture and strength at a time that is critical for developing healthy bones. Fracture rates are 2-3 times higher in children with CKD than the general population. The attendant morbidity and mortality associated with fractures in CKD has led to efforts to better understand their pathogenesis in order to develop and study treatments that improve bone strength while simultaneously providing an acceptable safety profile across the life-course. The lack of safe and proven antifracture pharmacologic strategies in children and adults with CKD represents a fundamental therapeutic gap in CKD management. We propose a pilot, 6-month, randomized clinical trial in 15 children and 88 adults with CKD stages 2 and 3 to test potassium citrate supplementation vs. placebo effects on bone strength as measured by high resolution peripheral quantitative computed tomography (HR-pQCT). We will also examine urinary net acid excretion and measures of bone turnover to understand how potassium citrate effects skeletal health. These aims will be achieved through the collaborative efforts of three institutions: Montefiore Medical Center/ Children's Hospital at Montefiore, University of Pittsburgh Medical Center / Children's Hospital of Pittsburgh, and Columbia University Irving Medical Center. The research team has the necessary expertise and resources to carry out this clinical trial. This study is innovative, as potassium citrate has never been tested in a randomized, placebo-controlled trial in chronic kidney disease in children and adults. Bone disease in pediatric kidney disease is understudied and this study will be an important first step to evaluating potassium citrate as a therapeutic agent. This pilot study will provide important information for design of a future larger U01 trial to evaluate effects of potassium citrate on bone outcomes across the life-course.

LAY ABSTRACT

Chronic kidney disease is associated with bone loss and fractures in both children and adults, but bone protective therapies that are both proven and safe to use across the life-course in CKD are lacking. In this study, we will conduct a pilot, double-blinded, randomized, placebo-controlled trial in 15 children and 88 adults evaluating the skeletal effects of potassium alkali therapy. These data will form the basis for a larger U01 proposal to determine the efficacy of potassium citrate on mitigating the effects of CKD on bone.

PROTOCOL

1. STUDY (PROTOCOL) TITLE

Bone In CKD Alkali Response Pilot Trial (BICARb Pilot Trial)

2. OBJECTIVES

The purpose of this study is to determine the effects of potassium citrate on bone quality and strength in patients with chronic kidney disease.

Our specific aims are:

Aim 1: To evaluate effects of potassium citrate treatment on bone quality and strength. We hypothesize that potassium citrate will improve bone quality and strength over 6-months. We will evaluate the between and within group differences in cortical and trabecular volumetric BMD, microarchitecture, tissue mineral density and mechanical estimates of bone strength measured by HR-pQCT after 6-months of alkali treatment.

Aim 2: To evaluate mechanism(s) underlying the effects of potassium citrate on skeletal health. *We hypothesize that acid neutralization by potassium citrate supplementation will decrease bone resorption to protect the skeleton.* **Aim 2a.** To assess the effects of potassium citrate supplementation on urinary net acid excretion (NAE). **Aim 2b.** To evaluate effects of potassium citrate supplementation on parathyroid hormone and circulating biomarkers of bone resorption (C-terminal telopeptides of type I collagen (CTX)) and formation (Procollagen type-1 N-terminal propeptide (P1NP)). **Aim 2c.** To determine the between and within treatment group relationships between serum bicarbonate, urine NAE, bone turnover markers and bone imaging.

Our investigative team includes expertise in pediatric and adult nephrology, metabolic acidosis, bone disease, kidney epidemiology and clinical trials. Success of either aim of this study will provide the groundwork for a multi-center clinical trial examining potassium citrate effects on bone strength. We expect that the knowledge gained from this study will highly impact the care of adult and pediatric patients for whom there are currently few available bone protective therapies.

3. BACKGROUND

CKD is a state of impaired bone quality and strength. Renal osteodystrophy (ROD) is present in the vast majority of CKD patients (1). In patients with versus without CKD: 1) Osteoporosis, defined as a T-Score ≤ -2.5 by dual energy X-ray absorptiometry (DXA) is 2-fold more common and 2) fractures are 2- to 14-fold greater and increase in parallel with CKD severity (2-6). In children, CKD significantly impairs bone strength at a time that is critical for developing healthy bones, resulting in fracture rates that are 2-3 times higher than in children without CKD (7-10). Moreover, despite treatment of CKD-MBD, >50% of adults who developed CKD in childhood reported skeletal symptoms, with 20% reporting handicaps from their bone disease (11). Further, in CKD patients with versus without fractures, mortality rates are doubled (6, 12). The morbidity and mortality associated with fractures in patients with CKD has led to efforts to better understand their pathogenesis and to develop treatments that improve bone strength while simultaneously providing an acceptable safety profile across the life-

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course. Bisphosphonates, the most commonly used osteoporosis medications, may be nephrotoxic (13), are potentially harmful to the skeleton in patients with late-stage CKD (14) and cannot be given to children. The lack of safe and proven anti-fracture pharmacologic strategies in children and adults with CKD represents a fundamental therapeutic gap in CKD management.

Metabolic acidosis (MA) is a major contributor to bone disease with CKD. In cell culture studies, chronic MA uncoupled bone remodeling and directly stimulated osteoclast-mediated bone resorption (15, 16). Our extensive pilot data showed that lower serum bicarbonate was related to abnormal bone quality: (1) In 55 CKD patients followed for a median of 1.5 years, decreases in serum bicarbonate were associated with trabecular drop-out as measured by high resolution peripheral quantitative computed tomography (HR-pQCT); and (2) among 22 CKD patients who underwent iliac crest bone biopsy with histomorphometry and micro CT assessment, lower serum bicarbonate was associated with elevated remodeling rates, trabecular erosion, and lower and more heterogeneous tissue mineral content. However, when sodium bicarbonate was used to correct MA in adults with CKD in Dr. Melamed's (MPI) randomized clinical trial, there was no improvement in bone mineral density (BMD) by DXA (17). This is in *stark contrast to kidney healthy patients – without acidosis but with a high acid generating western diet – who experienced improvements in bone density and quality measured by DXA and HR-pQCT, respectively, in response to potassium citrate treatment (18, 19). In contrast to sodium alkali, potassium alkali does not result in a calciuresis that could negate the beneficial skeletal effects of alkali neutralization of acid loads (20, 21).*

Chronic kidney disease (CKD) affects over 37 million individuals in the United States (US), and 752 million individuals worldwide (22). CKD stage 5 requiring dialysis or transplantation affects over 700,000 Americans. Renal osteodystrophy (ROD) is present in all these patients as well as in a sizeable fraction of the 37 million in the US with CKD stages 1-4. ROD severity worsens with declining kidney function, and it persists even after correction of kidney function with transplantation. Osteoporosis, defined as a T-Score ≤ -2.5 by dual energy X-ray absorptiometry (DXA) is 2-fold more common in patients *with* than without CKD (23), and among patients with osteoporosis the prevalence of moderate-to-severe CKD was ~ 80% for women and 50% for men >60 years of age (24). Thus, due to the high co-prevalence of CKD and skeletal disorders, it is not surprising that fractures are 2- to 14-fold greater in adults with than without CKD and increase in parallel with CKD severity (2-6). As the CKD population grows and as the population ages, fracture incidence in the US population will continue to increase exponentially (25).

CKD in childhood causes significant adverse effects on the growing skeleton, imparting life-long negative consequences. CKD-mineral bone disorder (CKD-MBD) and metabolic acidosis during growth and development cause early insults to skeletal integrity, resulting in bone deformities, increased fracture rates and poor linear growth. These negative sequelae affect the child during their entire life. Data from the largest study of children with CKD in North America (CKiD) demonstrated that: (1) Children with CKD have a 2-to 3- fold higher incidence of fractures than the general population (7); and (2) Children with $\text{CO}_2 < 18$ mEq/L had height SDS that was on average 0.67 lower compared to those with $\text{CO}_2 \geq 22$ mEq/L (26). Despite treatment of CKD-MBD, >50% of adults who developed CKD in childhood reported skeletal symptoms, with 20% reporting handicaps from their bone disease. (11) Therefore, safe and effective bone protective therapies are needed to mitigate the negative life-long

skeletal effects of CKD.

Fractures are debilitating injuries with prolonged rehabilitation, long-term pain, and increased costs. Only 50% of patients with a hip fracture regain their mobility and remain at their pre-fracture level of independence (27). As the population ages, predictions about increasing numbers of fractures are staggering from 1.7 million fractures to 6.3 million fractures between 1990 and 2050 (25). Studies in patients with CKD stages 3-4 (5, 28-30), on dialysis (4, 31), and after transplantation (32, 33) all demonstrate that patients with CKD compared to age- and sex-matched individuals without CKD have a 2- to 100-fold increase in fracture risk. A 40-year-old woman on dialysis compared to a 40-year-old in the general population has a 100-fold increased risk of having a hip fracture. Even at age 80, the risk in both men and women on dialysis compared to age and sex-matched individuals without CKD is more than 2- fold greater (32).

Moreover, despite treatments targeting the biochemical abnormalities of CKD-MBD, including vitamin D deficiency and elevated levels of circulating parathyroid hormone (PTH), fracture incidence of the appendicular skeleton more than doubled from 1992 to 2009 in patients with CKD stage 5 requiring dialysis (34). Mortality risk doubles in patients on dialysis who sustain a major fracture requiring hospitalization (12, 35) and healthcare associated costs after fracture in patients with CKD exceeded \$600 million in 2010 (6). Therefore, anti-fracture strategies are desperately needed to mitigate the effects of CKD and osteoporosis on morbidity and mortality.

There are no proven, safe strategies that prevent bone loss and fractures in adults or children with CKD. All strategies with potential use for bone protection in adults with CKD have been extrapolated from kidney healthy populations (36-39). Their use in CKD patients remains controversial and they are considered to have poor bone and kidney safety profiles by many nephrologists (13, 14). All safety and efficacy data on the use of anti-resorptives and anabolic agents are derived from *post-hoc* analyses of FDA trials that specifically excluded patients with CKD, vitamin D deficiency and hyperparathyroidism (i.e., CKD-MBD). However, by application of GFR estimation (eGFR) formulas some patients were identified as having low eGFR due to age related declines in function; whether they had true kidney disease has been highly debated. Moreover, the numbers of patients “with CKD” in the FDA trials were small, with some studies having had so few patients that valid statistical analyses based on standard CKD stages could not be conducted (37, 38). Recent data even suggests that use of oral bisphosphonates, the most commonly administered bone protective agent, may accelerate kidney function decline (13, 40). Furthermore, it is critical to note that there are no therapies that can be given to the growing skeleton. The lack of safe, proven anti-fracture pharmacologic strategies in children and adults with CKD represents a fundamental therapeutic gap in CKD management that this pilot study R01 will start to address.

Rigor of Prior Research and Preliminary Data: Bone biopsy and cell culture studies suggest that metabolic acidosis is associated with high bone turnover and abnormal mineralization. In adults with CKD, bone biopsy studies suggested that MA was associated with osteomalacia (41). Incubation of mouse calvariae at reduced pH suggested uncoupling of bone turnover favoring resorption, with suppression of collagen synthesis and alkaline phosphatase (i.e., suppressed markers of osteoblast function) in conjunction with a net increase in calcium efflux that was associated with increased osteoclast activity (15). Correction of acidosis in patients on hemodialysis

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improved bone turnover in patients with both low and high turnover disease (42). The effect of acidosis on bone tissue mineral density (TMD) and calcium content has not been explored. Therefore, we assessed relationships between serum levels of bicarbonate, dynamic and mineralization parameters from standard histomorphometry, TMD and calcium content from bone mineral density distribution (BMDD) in 22 pre- dialysis CKD patients who underwent transiliac crest bone biopsy as part of MPI Dr. Nickolas' study of bone quality and strength. Mean age was 63±14 years, eGFR 27±18 mL/minute, and 8%, 32%, 16% and 44% had CKD stages 2, 3, 4 and 5 respectively. Median (min-max) serum bicarbonate was 23.5 (19.0-31.0) mEq/L. Thirty-six percent of the cohort had high turnover osteodystrophy and none of the patients had low turn- over or adynamic bone disease. At the bone tissue level by histomorphometry, lower bicarbonate was related to a higher bone formation rate (rho -0.42 p=0.04). TMD, measured by micro-CT (resolution 5 µm), is the mineral content of bone excluding bone marrow and fat; it is an important component of bone strength. *We found that acidosis was related to lower mineral content (Table 2).* BMDD, measured by quantitative backscatter electron imaging (qBEI) of bone biopsy samples, characterizes both mineralization kinetics and the degree and distribution of bone mineral content: reflections of the speed of mineralization of newly formed osteoid and bone turnover respectively (43, 44). BMDD of cortical and trabecular bone is highly conserved, varies little by age, sex, race/ethnicity, or skeletal site, and is highly correlated with bone turnover and the age of the bone region of interest. *Lower bicarbonate levels were related to both a lower mean amount and more heterogeneous pattern of calcium content in trabecular and cortical bone (Table 2).* Both these abnormalities in calcium content and distribution within bone tissue are associated with decreased bone strength (45). These data suggest that acidosis results in abnormal bone quality, characterized by elevated bone resorption rates and demineralization. These bone tissue defects may play a critical role in the increased skeletal fragility of children and adults with CKD. We hypothesize that supplementing CKD patients with potassium alkali may mitigate the skeletal effects of lower bicarbonate levels and protect against fractures across the life-course.

Table 2: Spearman correlations between serum bicarbonate and bone biopsy based TMD by microCT and MDD by qBEI. Acidosis was associated with lower and more heterogeneous mineral content.

	Tissue Mineral Density	Trabecular Bone Mineral Density Distribution					Cortical Bone Mineral Density Distribution				
		CaMean	CaPeak	CaWidth	CaLow	CaHigh	CaMean	CaPeak	CaWidth	CaLow	CaHigh
Bicar-bonate	0.66	0.48	0.45	-0.79	-0.65	0.38	0.44	0.38	-0.58	-0.40	0.28
p-value	<0.01	<0.05	<0.05	<0.0001	<0.01	0.1	0.05	0.1	<0.01	0.08	0.2

CaMean, the weighted mean Ca concentration of the bone area obtained from the integrated area under the BMDD curve in units of [wt.% Ca]; CaPeak, the peak position of the histogram, which indicates the most frequently measured calcium concentration (Ca value with the highest number of pixels) in the bone area in units of [wt.% Ca]; CaWidth, the full width at half maximum of the distribution, describing the variation in mineralization density in units of [Δwt.% Ca] (Δ = differences of Ca concentrations); CaLow, the percentage of bone area that is mineralized below the 5th percentile of the reference range in units [% bone area], that is below 17.68 wt.% Ca, this parameter corresponds therefore also to the amount of bone area passing primary mineralization; CaHigh, the percentage of bone area that is mineralized above the 95th percentile of the reference range in units [% bone area], that is above 25.30 wt.% Ca, this parameter corresponds to the amount of bone area having achieved plateau level of mineralization (amount of fully mineralized bone matrix) and includes also the contribution of highly mineralized cement lines. (Manuscript under revision)

Acidosis is a frequent and early complication of pediatric CKD that has negative skeletal effects. Acidosis is common in childhood onset CKD due in part to the higher prevalence of kidney tubular dysfunction in the setting of congenital abnormalities of the kidney and urinary tract (CAKUT). In the CKD cohort, 18% of those with eGFR between 50-90 ml/min were on alkali therapy and this increased to 37% by CKD stage 4. When compared to those with eGFR ≥50 ml/min, children with eGFR between 30-49 ml/min had almost twice the risk of having serum bicarbonate levels below 21 mmol/l (46). In children with proximal renal tubular acidosis (RTA), but normal or

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minimally impaired kidney function, bone histomorphometric studies showed low bone formation and mineralization, which improved following correction of acidosis with alkali therapy (47). *Thus, data in children demonstrated that acidosis severely and negatively impacts the growing skeleton, and that correction improves bone mineralization and remodeling. Whether alkali supplementation results in a positive life-long impact on bone strength and fracture rates is unclear. Our proposal is the first step towards determining if potassium citrate administration will mitigate the skeletal effects of acidosis in children with CKD.*

Potassium but not sodium alkali therapy may protect the CKD skeleton across the life-course. Alkali therapy is standard of care for many adult and pediatric CKD patients and its safety profile is known. Potassium alkali has been demonstrated to have beneficial effects on bone density and quality in kidney healthy adults without acidosis (18, 19). The putative benefit is neutralization of acid generation from a protein rich western diet (~10-100 mEq protons daily) (48-50). Twenty-four months of treatment with potassium citrate vs. placebo resulted in a $1.7 \pm 1.5\%$ ($p < 0.001$) increase in areal bone mineral density (BMD) by DXA at the lumbar spine – an effect similar to what may be seen for bisphosphonate therapy in post-menopausal women (51). Furthermore, by high resolution peripheral computed tomography (HR-pQCT), potassium citrate vs. placebo resulted in a $1.3 \pm 1.3\%$ and $2.0 \pm 2.0\%$ (both $p < 0.001$) increase in trabecular volumetric BMD at the tibia and radius respectively and a $1.9 \pm 1.8\%$ increase in trabecular number at the radius. Of note, these effects were significant after only 6-months of treatment. These findings suggest that potassium alkali not only builds bone density but may have a bone anabolic effect. In contrast, sodium alkali may not benefit the CKD skeleton. In a double blinded randomized clinical trial (RCT) of 149 patients with CKD stages 3 and 4, MPI Dr. Melamed reported that sodium bicarbonate vs. placebo had no effect on BMD at the femoral neck in patients with moderate-to-severe CKD (17). Potassium but not sodium is associated with decreased urinary calcium excretion and an improvement in calcium balance (20, 21) and some studies even suggest that sodium alkali is associated with increased urinary fractional excretion of calcium (52). The potential hypercalciuric effect of sodium loading may negate the benefit of acid neutralization in patients with CKD.

HR-pQCT imaging can detect abnormal bone quality due to metabolic acidosis.

A clinical trial of 201 men and women ≥ 65 years, also discussed above, with healthy kidney function were randomized to potassium citrate or placebo (18). HR-pQCT was used to determine if alkali supplementation resulted in changes to microarchitectural features of bone quality. Patients randomized to alkali vs. placebo had improvements in trabecular density (tibia: $+1.3 \pm 1.3\%$, $p < 0.001$; radius: $+2.0 \pm 2.0\%$, $p < 0.001$), number (radius: $+1.9 \pm 1.8\%$, $p < 0.05$) and thickness (radius: $+1.5 \pm 1.6\%$, $p < 0.05$). The beneficial skeletal effect of potassium alkali administration was potent enough to be detected at 6-months of treatment, with significant increases detected for total volumetric BMD of the radius and tibia. There are no data in CKD patients on relationships between acidosis and measures of bone quality assessed by HR-pQCT. Thus, we evaluated whether acidosis was cross-sectionally and longitudinally associated with impairments in cortical or trabecular bone by HR-pQCT in CKD patients from Dr. Nickolas' study of bone quality and strength. One-hundred eighty subjects with CKD 3-5D and an age-, race, sex-frequency matched healthy reference population of 75 individuals underwent HR-pQCT imaging (XCT1, resolution $\sim 80 \mu\text{m}^3$) and had simultaneous blood assayed for standard metabolic parameters. To compare HR-pQCT measures between CKD patients with and without acidosis, we generated age-, race, sex- based Z-Scores based on the reference population. The cohort was 49% female and acidosis, defined

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as a bicarbonate ≤ 22 mEq/mL, was present in 31% of the cohort. *Patients with compared to without acidosis had lower total density (mean difference Z-Score -0.4 $p < 0.02$) and impaired trabecular microarchitecture characterized by lower trabecular number, more space between trabeculae and greater heterogeneity in the trabecular network at the tibia. A subset of 55 subjects had 1.5 (0.9-4.3) years follow-up, and decreases in serum bicarbonate, adjusted for eGFR, were associated with trabecular bone loss: each 1 mEq/L decrease in CO₂ resulted in a -0.05 lower trabecular number Z-Score ($p < 0.05$) at the radius. These critical data indicate that acidosis in CKD impairs bone quality and strength and provides the rationale that alkali supplementation may prevent acid induced loss of bone quality and strength. These data obtained with the lower resolution XCT1 ($\sim 80 \mu\text{m}^3$) suggest that in CKD, acidosis associated impairments in bone quality are detected non-invasively by HR-pQCT. Our proposal will use the *higher resolution* XCT2 (resolution $60 \mu\text{m}^3$), which is less biased by partial volume effects, permitting more accurate quantitation of defects in cortical (i.e., cortical pore number and size) and trabecular (i.e., directly measures trabecular number and spacing) bone. We anticipate that the XCT2 will elucidate mechanisms by which alkali supplementation improves bone quality at the microarchitectural level.*

Bone Turnover Markers. Experimental studies have shown that chronic metabolic acidosis uncouples bone remodeling, favoring osteoclast mediated bone resorption. The putative skeletal effect of elevated resorption is bone-tissue demineralization and cortical and trabecular microarchitectural decay. In adults with CKD, acidosis has also been shown to increase PTH levels; Thus, acidosis worsens bone deterioration. (53) While bone biopsy with tetracycline double labeling is the gold standard method to measure remodeling activity, it is not practical to obtain in clinical and research settings due to its invasiveness, time-consuming measures, and expense, and it is a marker of local rather than global remodeling activity. Circulating markers of bone turnover (BTMs) can reflect non-invasively global skeletal bone cell activity. The International Osteoporosis Foundation recommends that levels of serum P1NP and CTX be used as reference standards for bone formation and bone resorption, respectively in healthy adults. Elevated levels have been associated with bone loss and fractures in adults with CKD (23, 54, 55). Nickolas et al evaluated the ability of BTMs to discriminate fracture status in 82 patients with CKD stage 3-5, 23 of whom had a prevalent fracture (55). The highest tertiles of BTMs were independently and positively associated with prevalent fracture. As part of our pilot data, we evaluated differences in levels of P1NP and CTX in 255 subjects with and without acidosis (180 patients with CKD 3-5D and 75 healthy reference participants). Patients with compared to without acidosis had higher levels of intact PTH, P1NP and CTX, indicating increased bone turnover. However, the effect of alkali supplementation on these biomarkers is not known. In children with CKD, BTMs have not been systematically studied. Leonard et al. obtained tibia quantitative computed tomography scans, PTH, Bone specific alkaline phosphatase (BSAP) and CTX levels in 156 children with CKD [69 stage 2-3, 51 stage 4-5, and 36 stage 5D (dialysis)] and 831 healthy participants, ages 5-21 years.(9) Higher levels of PTH and markers of bone formation (BSAP) and resorption (CTX) were associated with lower cortical density and area and greater endocortical circumference ($r = 0.18-0.36$, all $p \leq 0.02$) – suggesting that elevated turnover was driving bone loss at the trabecular-cortical interface. In the CKD participants, lower serum bicarbonate levels were associated with greater CTX levels ($r^2 = -0.23$, $p < 0.01$) but not BSAP levels ($r^2 = -0.09$, $p = 0.27$) – suggesting that acidosis was associated with uncoupling of turnover, favoring resorption – even in childhood CKD. These significant associations persisted (all $p < 0.01$) after adjustment for CKD severity. (9) Similar to adults, in children with CKD, the effects of alkali supplementation on bone turnover biomarkers are unknown.

These critical data from the observational literature and our pilot data strongly support the premise of our proposal, that alkali supplementation will protect the skeleton ACROSS the life-course.

Summary. Bone loss and fractures are common co-morbid conditions in children and adults with CKD. Fractures cause increased morbidity, mortality, and increased health-care related expenditures. Despite the high risk and burden of fractures in patients with CKD compared to the general population, there are no FDA approved anti-fracture and bone protective therapies, and the use of current osteoporosis therapies is controversial, contraindicated or potentially associated with adverse kidney and bone outcomes. Potassium alkali supplementation, even in patients without overt acidosis, may provide an effective and safe intervention to protect the skeleton in both children and adults. The proposed pilot RCT will examine between and within group effects of potassium citrate administration in comparison to placebo on bone quality and strength as measured by HRpQCT. The pilot study will also examine relationships between potassium citrate and net acid excretion and bone turnover markers. These critical pilot data will inform the development and implementation of a large-scale efficacy trial on the role of potassium citrate to increase bone strength in children and adults with CKD, and to protect children with CKD from abnormal skeletal development.

4. SUBJECT SELECTION AND WITHDRAWAL

4.1. NUMBER OF SUBJECTS

We are going to screen up to 120 potential study participants to reach target enrollment of 88 adults and 15 children. We accounted for attrition rate of 15% in our sample size, so we do not plan to replace dropouts.

4.2. INCLUSION AND EXCLUSION CRITERIA

Table 3 contains the Inclusion and Exclusion criteria for the trial.

Table 3. Inclusion and Exclusion Criteria	
<i>Pediatric Inclusion</i>	<i>Adult Inclusion</i>
1) Children 5-17 years old	1) Adults ≥18 years old
2) Estimated eGFR ≥30 and <90 ml/min/1.73m ² by CKiD U25 (For Pediatric participants) equations	2) Estimated eGFR ≥30 and <90 ml/min/1.73m ² by the new CKD-Epi without race (For Adults)
3) Females of childbearing potential must have had a menstrual period in the last month	3) Pre-menopausal women of childbearing age must have had a menstrual period in the last month
4) PTH and alkaline phosphatase within 2x normal range, and phosphorus levels within the normal range for age (per local laboratory reference assay)	4) PTH and alkaline phosphatase within 2x normal range, and phosphorus levels up to 5.0 mg/dL (per local laboratory reference assay)
5) 25-hydroxyvitamin D ≥ 20 ng/mL	5) 25-hydroxyvitamin D ≥ 20 ng/mL
6) Females of childbearing potential must be willing to use one form of effective contraception over the course of the study	6) Women of childbearing potential must be willing to use one form of effective contraception over the course of the study

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7) Proficiency in English or Spanish	7) Proficiency in English or Spanish
8) For participants < 18 years, the participant and/or parent/guardian capable of providing informed consent and assent (assessed by the provider)	
Pediatric and Adult Exclusion	
1) Baseline potassium > or = 5.5 mEq/L or prior history of hyperkalemia in the last 6 months (potassium >5.5 mEq/L) or currently taking a potassium lowering agent	
2) Alkali therapy within the prior 12 months	
3) Baseline ECG with abnormalities associated with increased risk of arrhythmia, excluding left ventricular hypertrophy	
4) Baseline serum bicarbonate levels <17 or > or = 30 mEq/L	
5) Serum calcium <8.6 mg/dL, adjusted for serum albumin	
6) Significant comorbidity causing acid-base imbalance (e.g., active cancer requiring chemotherapy, chronic liver failure, moderate or severe chronic obstructive lung disease, New York Heart Association class 2 or greater congestive heart failure, obstructive sleep apnea requiring nightly continuous positive airway pressure, active glomerular disease requiring immunosuppressive therapy, intestinal malabsorption or celiac disease)	
7) Plans to relocate out of the area in the next 3 months	
8) Urine pH > 8 or history of nephrolithiasis	
9) Lower extremity amputations or non-ambulatory	
10) Metabolic bone disease not related to CKD (e.g., Paget's disease, primary hyperparathyroidism)	
11) Endocrinopathy: untreated hyper or hypothyroidism, Cushing's syndrome	
12) Medical diseases that can affect therapy (severe myocardial damage, acute dehydration, delayed gastric emptying, esophageal compression, or intestinal obstruction or stricture)	
13) Use of bisphosphonates, denosumab, teriparatide, abaloparatide, romosozumab, raloxifene, estrogen or testosterone replacement therapy, or an unstable dose of glucocorticoids within the 12-months prior to enrollment	
14) Previous bilateral wrist and tibia fractures	
15) Solid or liquid organ transplant	
16) On dialysis or with rapidly deteriorating kidney function or expectation for transplantation or initiation of dialysis in less than 3 months	
17) Pregnancy or breastfeeding	
18) Prisoners or institutionalized individuals	
19) Unwillingness to provide informed consent	

4.3. VULNERABLE POPULATIONS

Pregnant women and cognitively impaired adults will be excluded from the study. Children will be included. Fully informed, written consent will be obtained from their parent(s) or legal guardian(s), and informed assent will also be obtained from the capable pediatric participants.

5. SETTING

PARTICIPATING CENTERS

Recruitment sites:

- Montefiore-Einstein/ Children Hospital at Montefiore (New York)
- UPMC-Children's Hospital of Pittsburgh (Pennsylvania)

For patients recruited at Montefiore-Einstein, visit 2 and final study visit (Visit 5) will be performed at Columbia University Irving Medical Center (see Table referring to Schedule of Visits for associated procedures). All patients recruited at The University of Pittsburgh will have all procedures at the University of Pittsburgh.

Each site is responsible for obtaining an IRB reliance agreement to set up Columbia as the single IRB for the study; recruiting, enrolling, and conducting study visits as per the study protocol; completing case report forms, data entry, and other study documentation, as required, in a timely fashion (no later than 2 weeks from the completion of each study visit). Each site is also responsible for alerting the

Coordinating Center (Montefiore-Einstein) and the **IND holder** (Dr. Thomas Nickolas) to problems that arise in the study. The PIs of each participating/recruiting site is responsible for assuring that their staff follows the provisions of the protocol, the operations manual, and all study performance. All staff will be noted on the site's Delegation Of Authority (DOA) Log

Sites engaged in the research not involved in enrolling participants:

This study does not involve recruitment procedures neither at the University of Utah, NYU Langone Health and CUIMC. However, these sites will provide support to conduct the research as further described.

- University of Utah (Salt Lake City)
- Columbia University Irving Medical Center - CUIMC (New York)
- NYU Langone Health

Sites engaged in the research in a coordinating capacity:

MPIs from Einstein/Montefiore, University of Pittsburgh and CUIMC have been involved in all aspects of the BICARb Pilot Trial: Development of the Grant, study protocol, study-wide recruitment materials, including the creation of case report forms (CRFs).

IND holder: Dr. Nickolas is the IND holder.

Study Lead Site: CUIMC

Columbia University is the single IRB (CU sIRB), CUIMC has been designated as the lead site, such as management of single IRB activities, monitoring participating site activities to ensure compliance with the IRB-approved protocol, evaluating safety and efficacy, FDA record keeping, submitting amendments, IND Safety Reports and Annual Reports to the FDA, and submitting required reports to the CU sIRB. Dr. Rubin will serve as the principal site investigator for CUIMC. This sIRB will be transferred to Einstein.

Coordinating Center (CC): Einstein/Montefiore Medical Center

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The Coordinating Center (CC) for the BICARb Pilot Trial will be Einstein/Montefiore Medical Center. This team will be responsible for scientific and administrative study activities, including overall execution of the study, coordinating recruitment activities with the sites; conduct study procedures, staff training and verify certification of participating site staff; conduct site activation meetings; conduct data collection, data entry and maintenance of the REDCap database; track the performance of the clinical sites in meeting study goals for recruitment and in protocol adherence; and ensure the quality of the clinical measurements obtained; coordinating aspects of data management, analysis, quality oversight and data acquisition and analysis and publication; and communicating with the NIH and subcontract financial management.

CC staff will support setting the meeting agenda/preparation of meeting materials, suggesting committee assignments according to expertise and interest, facilitating committee tasks, tracking study progress, preparing written minutes, distributing materials, and scheduling meetings, setting the timetable for the regular the Data Safety and Monitoring Board (DSMB) meetings and reports.

The CC is the primary contact for the participating sites on all matters regarding participant eligibility, and any deviations from protocol. The CC will design and develop all data processes, and data quality control procedures, including the creation of case report forms (CRFs) and the development and maintenance of the study database; coordination of the production of the study operations manual; and direction of the collection of data, with the IND Sponsor's input and agreement.

Skeletal Coordinating Center (SCC): CUIMC

Columbia University Irving Medical Center has been designated as the Skeletal Coordinating Center. Dr. Rubin will conduct and oversight all bone biomarker tests, skeletal health related questionnaires, and skeletal imaging data acquisition, quality, analysis, interpretation, and publication. Ms. Sanchita Agarwal (Co-Investigator) will confirm that operators are trained and/or certified for scanning BICARb participants and arrange for cross-calibration of phantom scans for all HR-pQCT scanners at all Skeletal imaging sites (CUIMC and Pittsburgh).

Potential Participant population

We have identified 2,600 adult and 84 pediatric patients with a CKD stage 2 or 3 diagnosis and an outpatient visit with a nephrologist within 3 years at Montefiore/Einstein/CHAM. We have identified 260 pediatric patients with CKD stage 2 or 3 at UPMC/CHP. We are looking to recruit 3% of the eligible adult population and up to 4% of the eligible pediatric population. If recruitment in pediatric population is insufficient, we will add additional sites.

During the conduct of the study, participants will receive medical care from their primary nephrologist or internal medicine/ pediatric physician. The study will cover the costs of the study medication and assessments and procedures required only for this study. The participants and/ or their insurance company will be responsible for the costs of all items and services during the research study, which the participants would have received for their condition if they were not enrolled in this research study and/or that their physician believes are medically necessary to treat the participant.

Ensuring adherence to study protocol

We have a study protocol that will be reviewed with all study personnel. We will have monthly meetings to review any deviations from or amendment to the study protocol.

6. MULTI-SITE RESEARCH

All sites will have the most current version of the study plan, consent documents and HIPAA authorization. All sites agreed to rely on Columbia University as a single IRB.

Communication Plans:

Communication among all PIs (and the research team) will occur weekly through a web-based weekly meeting (zoom), as well as document sharing and email discussions. Communication will also occur through face-to-face meetings at the national meetings of the American Societies of Nephrology and Bone and Mineral Research. Since all the PIs are located in the Northeast region, they will arrange a bi-annual face-to-face comprehensive review of study procedures and progress, to occur a few weeks before the scheduled DSMB meetings. All modifications will be communicated to sites and approved (including approval by the participating site's IRB of record) before the modification is implemented. All engaged participating sites will safeguard data as required by local information security policies. All local site investigators will conduct the study appropriately, and any deviations from study protocols will be re-viewed monthly. We will try to remediate any issues resulting in deviation so that deviations do not recur. All non-compliance with the study plan (protocol) or applicable requirements will be reported in accordance with local policy.

Problems: Problems will be discussed at our weekly meeting. We will try to remediate any issues.

Interim results: Interim results will be reviewed with DSMB and the MPIs will follow any DSMB recommendations.

Closure of study: For premature study closure, all patients will be immediately notified by phone call, email or mail, and will be referred to their primary nephrologist.

7. RECRUITMENT METHODS

Albert Einstein College of Medicine

Eligible participants will be identified using both review of patients scheduled to see nephrology as well as a searchable electronic database at Montefiore/Einstein. Participants will be recruited from adult and pediatric nephrology clinics and/or internal medicine and endocrine clinics at Einstein/ Montefiore. We will allow for referred patients from other New York institutions to be recruited if they hear about the study from clinicaltrials.gov or through their nephrologist. Nephrology and Endocrinology healthcare providers at Einstein/ Montefiore will receive a "Dr to Dr letter" to inform them of the research. They will be able to identify possible participants eligible for inclusion during their in-person or Telehealth visits, introduce the study, and/or refer patients to Dr. Abramowitz (adult) or Reidy (pediatric) at Montefiore or Dr. Kumar at UPMC for a clinical assessment. We will use the electronic health records to identify potential subjects with ICD10 diagnosis of stage 2-3 CKD. We will also review electronic health records of patients scheduled to see internal medicine/ pediatric nephrologists for this diagnosis to identify eligible patients. A HIPAA waiver is being sought for this preparatory to research activity.

University of Pittsburgh - Children's Hospital of Pittsburgh (CHP)

The electronic health record will be used to identify potential subjects with an ICD10

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diagnosis of stage 2-3 CKD who are currently followed by the CHP pediatric nephrology providers. We will also review electronic health records of new patients scheduled to see the pediatric nephrology providers for this diagnosis to identify eligible patients. Nephrology healthcare providers at UPMC-CHP will receive a “Dr to Dr letter” to inform them of the research. They will be able to identify possible participants eligible for inclusion during their in-person or Telehealth visits, introduce the study, and/or refer patients to Dr. Kumar for a clinical assessment. A HIPAA waiver is being sought for this preparatory to research activity. Dr. Kumar will contact the primary nephrologist to notify them of the patient’s eligibility for the trial. With consent of the primary doctor, eligible participants will receive Columbia University IRB-approved flyers, in-person or via mail or email. The study coordinator will contact eligible participants to follow up by phone about the study. When possible, the study coordinator will meet the potential participants at their clinic visits to further explain the study and obtain informed consent. Virtual telemedicine will be used for all aspects of the study not requiring in person presence, as per patient preference.

PRE-CONSENT PHONE CALL

If menstrual history and contraceptive use is not available in EHR, a pre-screening phone call will be made to obtain this information from adult females and/or the parent of females aged 9 to 17. If this phone call is needed, verbal consent will be obtained. Payments to subjects: Participants will receive a debit card (ClinCard or equivalent) at the time of enrollment and payments will be added to the debit card for the duration of the study. Subjects will receive \$75 for each in person imaging visit, \$10 for each safety lab visit. And up to \$50 for each in-person non-imaging visits to compensate them for their time and offset travel costs. Total estimated compensation for all study visits is \$225, and up to an additional \$150 for safety labs.

8. STUDY TIMELINES

An individual subject is expected to be in the study for 8 months. We anticipate starting the enrolling subjects starting in November 2022 and participants completing the study in March 2025. We anticipate completing the analysis by June 2025. (See Table 4)

Table 4. Study Timeline									
TASK	2022-23			2023-24			2024-25		
	Months			Months			Months		
	7-10	11-2	3-6	7-10	11-2	3-6	7-10	11-2	3-6
Start-up planning, IRB	■								
Finalize protocol and RED-Cap database and create Manual of Operations	■								
DSMB Meeting			■			■			■
Train coordinators	■								
Dry-run for enrollment visits at all sites	■								
Recruitment		■	■	■	■	■	■		
On-going visits		■	■	■	■	■	■	■	
Assess study recruitment benchmarks			■		■			■	
Data cleaning and analysis							■	■	■
Manuscript preparation								■	■

9. PROCEDURES INVOLVED

This study includes the following procedures:

- **Medical record review:** Study staff will review participants' medical records throughout the study to collect information about medical history, current health, diagnosis, treatments, medications, results of clinical labs and/or tests.

Test	Window period
eGFR, K, Ca, HCO ₃	Within 3 months
PTH, P, 25-OH Vit D, Alkaline phosphatase	CKD 2: within 12 months CKD 3: within 6 months

- **Electrocardiogram:** To confirm that participants do not have any abnormal heartbeat, an ECG obtained within the 3 months prior to the screening visit will be acceptable for use; thus, ECG will be obtained only if participants don't have an ECG within the prior 3 months, or if they have hyperkalemia in the safety labs results (≥ 6.0 mEq/L).

- **Urine Collection:**

Pregnancy test: All childbearing potential female will undergo a urine pregnancy testing before starting this study and at each bone imaging visit. Pregnant women will be excluded from the study at any time point in order to protect the fetus.

Urine pH assessment: Urine pH will be measured by urine dip at the baseline visit, end of the run-in, and the 3- and 6-month visits.

Timed 24 Hour Urine Collection: Participants will be provided with urinary collection containers prior to their study or lab visits so that timed urine collections can be performed at home. 24-hour timed urine collections will only be performed in toilet trained children/adults who are able to perform a timed urine collection. Urine collection will be performed at home. We will suggest participants first empty their bladder and then perform the urine collection from 7 am until 7 am the following day. If a 24-hour urine collection is not possible in some participants, particularly in children, we will perform a shorter timed urine collection (e.g., 12 hour). 24-hour urine collections will be performed at the time of the baseline study visit (prior to potassium citrate therapy), at 3 months and at the concluding study visit.

- **Physical exam:** We will measure weight, height, and the length of participants' forearm (radius) and lower leg (tibia) at several points of the study. We will include blood pressure (BP) measured in triplicate. For children who have not already reached Tanner V prior to enrollment, pubertal status will be assessed by self-assessment if not documented in the medical record in the past 2 months. Height, weight, limb length and anthropometric data (see below) will be obtained for all participants.
- **Surveys and Questionnaires:** This study includes multiple surveys and questionnaire, some of them will be completed by phone, zoom video call, through a website link, and/or in-person. We will also collect information by questionnaires and chart review at enrollment and follow-up visits. Questionnaires will include age, sex, race/ethnicity, highest level of education completed (participant or parental), household income, smoking exposure, kidney disease etiology and kidney function, including albuminuria, birth and

family history, quality of life questionnaires and medication use. We will also obtain information on medical history; assessment for fracture history by questionnaire and review of any radiographic records; physical activity questionnaire; 1 day dietary questionnaire; medication review, including exposure history for: antihypertensives, potassium binders, alkali medications, corticosteroids, calcineurin inhibitors, vitamin D (nutritional and active), diuretics, cinacalcet; self-report of medication adherence; health related quality of life measurements using the SF36 (Adult) or the Pediatric Quality of Life Questionnaire (pediatric).

Tolerability assessment: At enrollment, the end of the run-in period, and during phase 2 (i.e., washout period and at all visits and monthly remote visits), a tolerability assessment by questionnaire will be conducted. The questionnaire will assess for gastrointestinal side effects (nausea, vomiting, abdominal pain, diarrhea, flatulence) as well as for symptoms of hyperkalemia (burning or tingling sensation, weakness, mental confusion, low blood pressure, or irregular heart rhythm). In addition, participants will be instructed to notify a member of the research team immediately for any of these symptoms at any time during the study.

- **Research blood sampling:**

For safety labs: Blood samples for safety labs are obtained to monitor the effect the study drug. For both children and adults, approximately 1 teaspoon (5 ml) will be collected.

For phase 1, participants will have blood draws at the baseline study visit and at 2- 5 days after starting potassium citrate. If serum potassium is elevated, adjustments to dose will be made and blood work repeated 2-5 days after the dose change. If serum potassium is <5.5 mEq/L, blood will be repeated in 2 weeks. To enter phase 2, participants will need 2 blood tests with a serum potassium <5.5 mEq/L two weeks apart. The participants will then undergo a 2-week washout prior to phase 2, where they will be randomized to potassium citrate (at the dose tolerated during run-in phase) or placebo.

For phase 2, blood will be obtained 2-5 days following the randomization, at 3 months and at the concluding study visit which will occur at the end of the 6 months study phase (i.e., Study Phase 2). If the serum potassium is elevated following randomization or at the 3-month visit, a dose change will be made, and blood work repeated 2-5 days after the dose change. In addition to bloods for safety testing, **blood for biobanking** will be stored at -80° at Einstein/Montefiore Biorepository.

For biobanking: Blood samples will be collected several times during the study. The amount of blood will depend on participant's weight. If it is more than 40 kilo- grams (kg), we will ask for up to 80 mL (a little more than 5 tablespoons). If it is between 20-40 kg, approximately 2 ½ tablespoons (up to 37 ml) of blood will be collected. In all instances, blood drawn for children will not exceed 5 ml per kg.

Blood will be drawn by the principal investigator (PI), an appropriately trained and delegated member of the study team, or by a trained phlebotomist. All specimens collected will be frozen at minus 80 degrees centigrade for analysis at a later date. Because these tests are experimental, the results will not be shared with participants or their treating physician and will have no impact o

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their routine care. Blood will be used to run all analysis related to this study (biochemical analysis, bone markers, etc.), for potential genetic studies, and future studies.

For Monitoring labs: Blood samples to monitor PTH, phosphate, 25-OH Vitamin D, and alkaline phosphatase will be collected at 3- and 6-month visits.

- **Skeletal imaging: High resolution peripheral quantitative computed tomography (HR-pQCT)**

Skeletal imaging (Figure 2)

High resolution peripheral quantitative computed tomography (HR-pQCT) of the distal radius and tibia for assessment of volumetric BMD, geometry and microarchitecture will be performed at enrollment and completion of the study.

HR-pQCT

Tibia and radius scans will be obtained on the non-dominant side unless

Figure 2.
HR-pQCT Configuration for the Tibia Scan



there is a reason to image the dominant side (e.g., prior fracture on non-dominant side). Two to three sets of images will be obtained, with a distal and midshaft scans in the tibia and radius. The acquisition of each scan requires 2 minutes. A custom hydraulic chair is used to position the participant and the limb is secured in a carbon cast that attaches to the scanner gantry (Figure 2). Scans will be evaluated for movement artifact and re-peated up to once at each anatomic site if necessary. In light of the participant positioning required for each scan, and the need for scout views and repeat scans in the event of movement, the study procedures can require up to an hour total. The radiation exposure for each scan is low.

- **Randomization and Treatment.**

Intervention

We will use **Potassium Citrate**

Adults and those able to swallow pills: Potassium Citrate extended-release tablets 30 mEq twice daily (1 mEq/kg/day divided into two doses for children to a maximum dose of 30 mEq twice daily). These pills are F.D.A. approved since 1985 in the U.S. for the following conditions:

1. Renal tubular acidosis (RTA) with calcium stones
2. Hypocitraturic calcium oxalate nephrolithiasis of any etiology
3. Uric acid lithiasis with or without calcium stones

Children not able to swallow pills: Potassium citrate and citric acid for oral solution 1 mEq/kg/day divided into two doses to a maximum dose of 30 mEq twice daily.

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Potassium Citrate and Citric Acid Oral Solution USP contains in each teaspoonful (5 mL):	
Potassium Citrate Monohydrate	1100 mg
Citric Acid Monohydrate	334 mg
Potassium Citrate and Citric Acid Oral Solution USP is not FDA approved but is used to treat children with renal tubular acidosis and nephrolithiasis as standard of care. Potassium Citrate and Citric Acid Oral Solution USP is a stable and pleasant-tasting oral systemic alkaliizer containing potassium citrate and citric acid in a sugar-free, non-alcoholic base. Each mL contains 2 mEq potassium ion and is equivalent to 2 mEq bicarbonate (HCO_3^-). Inactive Ingredients: FD&C Red No. 40, flavoring, polyethylene glycol, propylene glycol, purified water, sodium benzoate, and sorbitol solution.	

Matching active medications and placebo pills will be manufactured by the Research Pharmacy at Einstein/ Montefiore and Investigational Drug Services at University of Pittsburgh Medical Center (UPMC) Children's Hospital of Pittsburgh.

Study drug adherence. Pill counts (or weighing bottles in case of solution) will be used to monitor adherence. Adherence will be assessed by pill counts or weighing bottles (for solutions) with study medications prior to dispensing and at the study completion visit. Weights will be compared to the expected consumption.

10. STUDY DESIGN AND STUDY VISITS

Intervention (Figure 1)

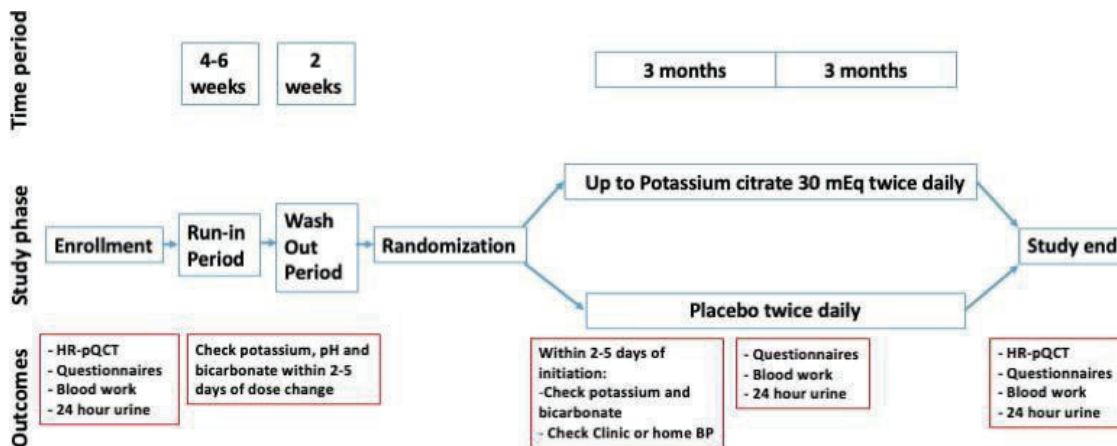


Figure 1. Study Activities for in Bone In CKD Alkali Response Pilot Trial (BICARb Pilot Trial)

This study includes five study visits that will be completed in-person and remotely thought different study phases/periods.

Screening visit (Visit 1 Screening; 1 day duration). After consent is obtained, we will collect baseline study information as itemized in the Table for Schedule of Study Procedures (Table 5). An in-person screening visit will be conducted to assess the potential study participant's adherence to the eligibility criteria. At this visit we will assess for pregnancy in women of childbearing potential by urine pregnancy test, for abnormalities associated with risk of arrhythmia (except left ventricular hypertrophy) by ECG, for urine pH > 8.0 by urinalysis and for baseline hyperkalemia by blood test. For ECG assessment, any ECG obtained within the 3 months prior to the screening visit will be acceptable for use; thus, ECG will be obtained only in those potential participants without a prior ECG within the prior 3 months. Labs will be reviewed, including intact PTH, alkaline phosphatase, phosphorus and 25-hydroxyvitamin D. For potential participants with CKD Stage 2, we will accept labs obtained within the 12 months prior to enrollment. For potential participants with CKD Stage 3, we will accept labs obtained within the 6 months prior to enrollment. Potential participants without labs within the a priori defined CKD Stage specific timelines will be referred back to their primary nephrologist for lab measurement as part of their routine clinical care. These patients can be re-screened at a later date. If a participant consents to the study, but does not meet eligibility at the time of the screening visit, they can repeat screening tests at later date to see if they meet eligibility requirements at that time.

Management of medications and supplements used to treat CKD-mineral and bone disease. If potential participants are on vitamin D and calcium prior to enrollment, they will be maintained and continued on their vitamin D and calcium supplements for the duration of the study. The dose of vitamin D and calcium will not be changed during the study. We will not start vitamin D in those patients who are not on vitamin D at study entry. We will not initiate calcium supplementation unless a study participant has hypocalcemia (biochemical and/or symptomatic).

Instructions on how to take the study drug. All study participants will be instructed to take the study drug (active drug or placebo) with meals or within 30 minutes after meals, or bedtime snacks to decrease the incidence and severity of GI side effects associated with potassium citrate.

Phase 1 of study (Visits 2, 2- week duration; Visit 3 Run-in phase, 4-6- week duration). Within 3 weeks s after the screening visit, participants will undergo a study visit 2 with a remote and in-person component (Table 5). If visit 2 cannot be scheduled within 3 weeks due to logistical issues, it can be schedule between 3 weeks to 3 months after screening, otherwise the patient will be rescreened. The remote portion will include ascertainment of demographics and completion of questionnaires. The in-person component will include a pre-skeletal imaging urine pregnancy testing in women of childbearing potential, HR-pQCT, and a processing of the 24-hour timed urine collection in those who are capable. In those unable to complete a 24-hour urine (e.g., young children), we will perform a shorter timed (e.g., 12 hours) urine collection.

For the run-in phase, all participants will receive potassium citrate. Adult participants will receive K-citrate (60 mEq/d, 10 mEq per tablet, three tablets twice daily). For children, we will give 1 mEq/kg/day divided into a twice a day dosing schedule. Children who cannot swallow K-citrate pills will be given K-citrate as a commercially

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available solution.

For safety, a simultaneous venous blood gas pH, serum potassium, creatinine, calcium, and bicarbonate will be obtained 2-5 days after starting the medication. If the serum potassium is 5.5-5.9 mEq/L or a serum bicarbonate >30 mEq/L, the dose will be decreased by 50% and participants will have repeat blood work after 2-5 days. If the serum potassium is ≥ 6.0 mEq/L, the study medication will be held, a potassium binder will be given, and serum potassium will be repeated within 24 hours. If potassium is improved, subjects will be given the study medication at 50% of the original starting dose and blood work will be repeated after 2-5 days. If the potassium is improved, we will stop the potassium binder and repeat blood work again after 2-5 days. Participants who cannot tolerate 50% of the total dose and/or with recurrent potassium >5.5 mEq/L will be withdrawn from the study. All participants who develop hyperkalemia will be referred back to their primary nephrologist to pursue a work-up and further treatment for hyperkalemia as appropriate. In addition, all participants who develop hyperkalemia will be counseled on a low potassium diet. As participants will not have severe kidney function impairment, we do not expect significant issues with hyperkalemia. In addition, alkali may lower serum potassium and prevent hyperkalemia, as was shown in Dr. Melamed's study, where 40% of participants on placebo experienced hyperkalemia (>5.0 mEq/L) compared to 19% on sodium bicarbonate (17). If a patient has clinical labs (separate from the study visits) that show hyperkalemia, we will follow the same protocol. Furthermore, all subjects will be given a card which will identify them as a participant in this clinical trial and will provide instructions to contact the study team in the event of hyperkalemia.

Participants will need 80% adherence to medications and 2 serum potassium levels of <5.5 mEq/L two weeks apart to enter the randomization phase. This run-in phase will determine the individualized dose (mEq of citrate) for each patient.

Phase 2 of study (Visits 4 at 3 month and 5 at 6-month after starting the study drug, Randomized Clinical Trial; 6 months duration).

Following the run-in phase, participants will undergo a washout of 2 weeks and will then be randomized to placebo or their individualized dose of K-citrate in a 1:1 fashion. Randomization will be performed by the research pharmacy at Montefiore. They will stratify by: (1) Study site to ensure that both pediatric centers will have equal numbers of subjects on potassium citrate and placebo (AECOM will have 8 participants and Pitt will have 7 participants); (2) For adults, by age < 55 and ≥ 55 years to ensure that there is an equal distribution of ages between active drug and placebo groups; and (3) For all participants, baseline bicarbonate levels by bicarbonate 17-24 mEq/L and 25-30 mEq/L to ensure equal distribution of bicarbonate levels between active drug and placebo groups. We will have 7 blocks of 4 = 28 participant randomization assignments within each stratum. Placebo pills and liquid will be identical and taste similar to the active comparator. The pharmacy will place the medications into capsules so that participants will receive an identical number of capsules (regardless of dose or treatment arm) so that both investigators and participants will remain blinded. Children who cannot swallow K-citrate pills will be given K-citrate as a commercially available solution. Similarly, equal volumes of suspensions will be prepared for all treatment arms to maintain blinding.

For safety, a simultaneous venous blood gas pH, serum potassium, creatinine, calcium, and bicarbonate and blood pressure measurement will be obtained 2-5 days after starting the medication. If the serum potassium is 5.5-5.9 mEq/L or a serum bicarbonate >30 mEq/L, the blinded dose will be decreased by 50% and participants

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will have repeat blood work after 2-5 days. If the serum potassium is ≥ 6.0 mEq/L, the study medication will be held, a potassium binder will be given, and serum potassium will be repeated within 24 hours. If potassium is improved, subjects will be given the study medication at 50% of the original starting dose and blood work will be repeated after 2-5 days. If the potassium is improved, we will stop the potassium binder and repeat blood work again after 2-5 days. For participants who cannot tolerate 50% of the total dose and/or with recurrent potassium >5.5 mEq/L, study drug will be discontinued but participants will remain in the study and complete all study procedures. Participants who develop hyperkalemia will be referred back to their primary nephrologist to pursue a work-up and further treatment for hyperkalemia as appropriate. In addition, participants who develop hyperkalemia will be counseled on a low potassium diet. If a patient has clinical labs (separate from the study visits) that show hyperkalemia, we will follow the same protocol. Also, serum 25-hydroxy-vitamin D, intact PTH, phosphate, and alkaline phosphatase levels at the 3- and 6-month study visits to ensure that levels remain stable compared to baseline.

Please see **Figure 3** for schedule of procedures/visits for across the duration of the investigation

Phase of trial	Phase 1														Phase 2					
	Screen Visit				Run-in period	Wash out	Randomization	Phone visits	Treatment											
Duration	1 day	2-3weeks			4-6 weeks	2 weeks	End of Wash-out	Monthly during Phase 2	6 months											
Visit	V1	V2			V3				V4 (at 3 months)			V5 (at 6 months)								
Type of visit		Remote Portion	In-person		In-person			Remote	Remote Portion	In-person Portion	Remote	In-person								
Performance site	Einstein/ Pitt	Einstein/ Pitt	Einstein/ Pitt	CUMC/ Pitt	Einstein/ Pitt	Einstein/ Pitt	Montefiore Pharmacy Einstein	Einstein/ Pitt	Einstein/ Pitt	Einstein/ Pitt	Einstein/ Pitt	Einstein/ Pitt	CUMC/ Pitt							
Screening: recruitment	X																			
Consent form	X																			
ECG	X																			
Pregnancy Test *	X			X										X						
Assessment of PTH, Phos, 25D, alkaline phosphatase-Monitoring labs	X									X			X							
Demographics, medical history: Collected by self-report questionnaire & chart review		X																		
Medication reconciliation form		X							X		X									
Height, weight	X									X			X							
Tanner Stage+	X																			
A one-day dietary history		X							X		X									
Blood pressure (triplicate)	X				X					X			X							
Quality of life assessment: SF36 (Adult)		X							X		X									
Pill counts or weighing bottles					X**					X			X							
24/12-hour urine collection instructions	X						X			X										
24/12-hour urine process and shipping to Utah			X							X			X							
Potassium Citrate ***			X																	
Tolerability Assessment by Questionnaire		X			X**	X		X	X		X									
Urine pH	X				X**					X			X							
Safety Labs: Creatinine, calcium, Simultaneous venous blood gas, serum potassium, and bicarbonate. Repeat 2-5 days after any dose adjustment	X****						X****			X****										
No use of medication						X														
Randomization to placebo or K-citrate by Pharmacy based on run-in dose							X													
Collection of research blood samples	X									X			X							
HR-pQCT & Limb length				X										X						
Study compensation (Einstein)	\$25			\$75	\$10+				\$50	\$10+				\$75						

+ Tanner staging by self-report only in children who have not reached Tanner V prior to enrollment, and if it is not documented in the medical record in the past 2 months.

**Results obtained at the screening visit and prior to each bone imaging.

***Completed at the end of the run-in phase

****Adults: 60 mEq/d, 10mEq per tablet, three tablets twice daily; Children: 1 mEq/kg/day divided into twice daily dosing to maximum of 60 mEq/day

*****Safety labs will be obtained at screening visit and 2-5 days after starting the study medication. \$10+ for each time Safety labs are required for the study purposes (up to \$150).

1. If the serum potassium is $5.5-5.9$ mEq/L, or serum bicarbonate >30 mEq/L, the dose will be decreased by 50% and participants will have repeat blood work after 2-5 days.
2. If the serum potassium is ≥ 6.0 mEq/L, the study medication will be held, ECG obtained, a potassium binder given and serum potassium repeated within 24 hours. If potassium is improved, subjects will be given the study medication at 50% of the original starting dose and blood work will be repeated after 2-5 days. If the potassium is < 5.5 mEq/L, we will stop the potassium binder and repeat blood work again after 2-5 days.
3. Participants who cannot tolerate 50% of the total dose and/or with recurrent potassium >5.5 mEq/L, will be withdrawn from the study.
4. If the serum potassium is < 5.5 mEq/L, it will be repeated in 2 weeks and follow the safety operating procedures.

Other Data Collection:

- We will use electronic medical records and questionnaires to collect data about subjects. Information will be gathered in person or via phone/ electronic methods/ email.
- We do not currently have plans to collect long-term data, but we will ask participants if they are willing to be contacted in the future for **long-term follow-up**.

11. SPECIMEN BANKING & GENETIC TESTING

Specimens (urine and blood) will be bio-banked at study visits 2,4 and 5. Specimens will be stored at the Einstein Biorepository at the Institute for Clinical and Translational Research. Data will include study subject identification and study visit date. The multiPIs will evaluate requests for use, and the multiPIs will adhere to National Institutes of Health regulations regarding NIH funded studies. Data and specimens will be stored indefinitely.

Blood specimens will be obtained and stored the Einstein Biorepository at the Institute for Clinical and Translational Research for potential genetic studies.

12. DATA MANAGEMENT

12.1. Data Analysis

Aim 1: To evaluate effects of potassium citrate treatment on bone quality and strength.

Aim 1 Analysis Plan and Statistical Considerations. We will perform analyses of cross-sectional and longitudinal bone data in children and adults, including strategies to adjust for age, sex and body size (e.g., cortical structure relative to tibia/radius length). Participant characteristics and study outcomes at each visit will be summarized as means with standard deviations or medians with interquartile ranges for continuous variables and as frequencies and percentages for categorical variables. Within each group, between-visits (baseline and 6 months) change in HR-pQCT measures, using standardized Z-Scores, will be assessed using the paired t-test or the Wilcoxon signed rank test, depending on the distribution of data. We will use transformations when appropriate for statistical techniques that rely on normality assumption. Analysis of covariances will be utilized to assess whether effects of potassium citrate on changes in HR-pQCT measures vary with eGFR and sex. Separate exploratory analyses will be performed in women and men (sex as a biological variable) and in pediatric patients. Adjustment for Tanner stage in children will be viewed as exploratory since categories of Tanner stage may be limited in the pilot study. We will use two-sided tests of hypotheses and p-value <0.05 as the criterion for significance. All analyses will be based on the intention-to-treat principle in which any participant randomized to a treatment remains in it regardless of adherence to or completion of treatment. This minimizes bias introduced by analyzing only adherent participants.

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Comparison of bone density, microarchitecture, and strength by HR-pQCT

Primary Analysis. Analyses of the between-treatment 6-month change (absolute) in Z-Score for radius and tibia total volumetric BMD will be conducted to determine if treatment effects are evident at and/or modified by weight-bearing and non-weight-bearing sites.

Secondary Analysis. We will evaluate between treatment group changes in discrete components (mechanisms) of bone quality and strength measured by HR-pQCT, including

cortical and trabecular volumetric BMD microarchitecture and geometry, cortical tissue mineralization density and bone strength (failure load) at baseline and over time in potassium citrate and placebo groups. We will implement a series of models as shown in **Table 5** with their anticipated results and putative disturbances in bone remodeling and mineralization. Given highly significant sex by- Tanner stage interactions for bone density and structure in healthy adolescents, the HR-pQCT analyses need to be adjusted for Z-Scores and Tanner stage, which is beyond the scope of this pilot study with limited sample sizes. The multivariable analyses adjusting for these factors will be performed in the future larger study if the Z-scores and Tanner stages differ between randomized groups.

Sample Size and Justification (Including Power Analysis) is based on a fixed sample size of 37 adult patients in the potassium citrate group and 37 adult patients in the placebo group.

All bone outcomes will be analyzed as Z-Scores to account for age, sex, and race. All models will be adjusted for eGFR. Bone strength and geometry measures adjusted for limb length group difference in changes between baseline and 6 months in HR-pQCT trabecular volumetric BMD at the radius based on Jehle et al (18). We assume that the mean percent change of HR-pQCT trabecular volumetric BMD is 0.9% in the potassium citrate group and -0.1% in the placebo group between baseline and 6 months (18). With $n = 74$ (37 in the potassium citrate group and 37 in the placebo group), the study will have 80.8% power to detect differences in mean percent change of HR-pQCT trabecular volumetric BMD between two treatment groups over 6 months, with a SD of 1.5% for the outcome, using a two-sided t-test and a type I error rate of 5%. The estimated effect size of 0.67 ($= (0.9 - (-0.1))/1.5$), which is the minimum detectable between group relative difference between estimated and assumed outcome to SD, corresponds to a large effect size, but the exploratory results from this pilot study will

Table 5. Hypothesized Longitudinal Within and Between Treatment Group Associations with HR-pQCT Outcomes of Bone Strength, Microarchitecture & Geometry

HR-pQCT Outcome	Placebo	Potassium Citrate	Putative Mechanism in Potassium Citrate Group
Bone Strength			
Radius failure load	↓ gains / ↑ loss	↑ gains / ↓ loss	↓ resorption
Tibia failure load	↓ gains / ↑ loss	↑ gains / ↓ loss	↓ resorption
Microarchitecture			
Cortical vBMD Porosity Tissue mineral density	↓ gains / ↑ loss ↑	↑ gains / ↓ loss +	↓ resorption ↓ resorption ↑ mineralization
Trabecular Thickness Number	↓ ↓	↑ ↑	↑ formation ↓ resorption
Cortical Geometry			
Endosteal circumference	↑	+	↓ resorption
Periosteal circumference	↓ gains / ↑ loss	↑ gains / ↓ loss	↑ formation

All bone outcomes will be analyzed as Z-Scores to account for age, sex and race. All models will be adjusted for eGFR. Bone strength and geometry measures adjusted for limb length.

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be viewed as preliminary and used to design a future larger study. Accounting for an attrition rate of 15%, 88 subjects will be enrolled and randomized in a 1:1 ratio to receive either potassium citrate or placebo (44 in the potassium citrate group and 44 in the placebo group). Sample sizes and power based on different assumptions are shown in **Table 6**.

Table 6. Sample size and power with different assumptions				
Attrition	Sample size per treatment before/after attrition	SD	α	$1 - \beta$
10%	36/32	1.4%	0.05	0.80
15%	38/32	1.4%	0.05	0.80
20%	40/32	1.4%	0.05	0.80
10%	42/37	1.5%	0.05	0.81
15%	44/37	1.5%	0.05	0.81
20%	47/37	1.5%	0.05	0.81
10%	47/42	1.6%	0.05	0.81
15%	50/42	1.6%	0.05	0.81
20%	53/42	1.6%	0.05	0.81

Aim 2: To evaluate mechanism(s) underlying the effects of potassium citrate on skeletal health. We hypothesize that acid neutralization by potassium citrate supplementation will decrease bone resorption to protect the skeleton. Aim 2a. To assess the effects of potassium citrate supplementation on urinary net acid excretion (NAE). Aim 2b. To evaluate effects of potassium citrate supplementation on parathyroid hormone and circulating biomarkers of bone resorption (C-terminal telopeptides of type I collagen (CTX)) and formation (procollagen type-1 N-terminal propeptide (P1NP)). Aim 2c. To determine the between and within treatment group relationships between serum bicarbonate, urine NAE, bone turnover markers and bone imaging.

Aim 2 Analysis plan and statistical approach: General preliminary approaches to data will include computing appropriate descriptive statistics and inspecting special features and patterns of data. This will determine whether transformations of data need to be done in further analyses. Changes in NAE, PTH, P1NP, and CTX from baseline to 6 months for each treatment group will be examined using paired-t tests or Wilcoxon signed rank tests as appropriate. Differences in changes in mean NAE, PTH, P1NP, and CTX from baseline between the two treatment groups will be compared using t-tests or Wilcoxon rank-sum tests as appropriate. Analysis of covariances will be used to examine effects of potassium citrate supplement on changes in NAE, PTH, P1NP, and CTX varying with sex adjusted for relevant prognostic factors (e.g., eGFR and serum bicarbonate). Spearman correlation coefficients will be calculated to assess correlation between serum bicarbonate, urine NAE, bone turnover markers and measures of bone quality and strength by HR-pQCT for each treatment group and in all participants. Mixed effects models will be used to examine whether associations of NAE with CTX and P1NP vary with time and treatment. In this model, NAE will be included as a time-dependent covariate. Random subject effects will be included into mixed models to account for the correlation of data. Mixed effects models will also be performed to examine if associations of CTX and P1NP with bone quality and strength measured by HR-pQCT vary with treatment adjusted for within-patient correlation. In these models, CTX and P1NP will be included as time-dependent covariates. If data allows, separate analyses will be performed in pediatric patients. All analyses will be based on the intention-to-treat principle in which any participant randomized to a treatment remains in it regardless of adherence to or completion of treatment. We will measure the level of participation and conduct a sensitivity analysis that assesses the stability of the conclusions from this study with an intention to- treat analysis versus an analysis that takes into account level of compliance.

Sample size and power:

Aim 2a: Jehle et al (18) reported mean $\pm$ SD 24-h urinary net acid excretion (NAE)

changed from 36.7 ± 16 ($n = 100$) at baseline to 32.9 ± 14.1 ($n = 88$) at 6 months in the placebo and changed from 38.6 ± 18.8 ($n = 101$) at baseline to -6.3 ± 24 ($n = 89$) at 6 months in the K-citrate. Assuming an attrition rate of 15% by 6 months, 37 of 44 participants in the potassium citrate group and 37 of 44 participants in the placebo group will have 24-h urinary NAE measured both at baseline and at 6 months.

For sample size and power calculation, we further assume mean 24-h urinary NAE is 32.9 at 6 months in the placebo group. Using the above results, a sample size of 37 participants per group will have 91.5%, 84.6%, or 80% power, for a low correlation ($\rho=0.2$), a moderate correlation ($\rho=0.5$), or a high correlation ($\rho=0.7$) among repeated observations, to detect a minimum difference in mean 24-h urinary NAE of 14.4 between the two treatment groups over 6 months at a 0.05 significance level, assuming a common standard deviation of 24.

Aim 2b: We anticipate an increase or no change in bone resorption marker CTX in the placebo group over 6 months. A sample size of 74 participants (37 in the potassium citrate and 37 in the placebo) will have 80% power to detect a difference in mean change in serum bone resorption marker CTX of 0.66 standard deviations (equivalent to a 0.66 effect size) between two treatment groups from baseline to 6 months using a two-sided t-test and a type I error rate of 5%.

Aim 2c: With a sample size of 74, the study will have sufficient power to detect weak to moderate positive (or negative) correlation between serum bicarbonate, urine NAE, bone turnover markers and measures of bone quality and strength by HR-pQCT. For example, we have 80.3% power to detect a weak correlation of 0.32 between urine NAE and bone resorption marker CTX at a two-sided 0.05 significance level under the null hypothesis of no correlation.

General Statistical Considerations (Aims 1 and 2): Missing data and loss to follow-up are usual concerns in longitudinal studies, presenting problems in interpretation with any approach. The validity of the resulting inferences depends critically on the underlying mechanism that generates the missing observation. If the mechanism for missing data is not a function of the underlying missing data, then no adjustment is necessary. Data that are missing at random will yield estimates from the likelihood-based methods that are valid and efficient, provided the model assumed for the data distribution is correct. However, when missing data are related to study treatment or outcomes of interest, parameter estimates and resulting tests on hypotheses will be biased without further adjustment. In this study, data will be stratified according to their missing pattern (e.g., early termination, late termination, and complete follow-up) and then variables based on these groups will be used as model covariates. This approach will allow us to examine the effects of missing-data patterns on the outcome measures. Overall estimates can be obtained by averaging over the missing patterns. Additionally, multiple imputations will be used if missing data rates are observed to differ across observed covariates. Regardless of the technique employed, the characteristics of participants that are lost to follow up will be compared to those that remain in the study.

12.2. Study Endpoints

The Primary Endpoint for Aim 1 is Total volumetric bone mineral density at 6 months. We will examine between treatment group changes (absolute, percent) for potassium citrate in distal radius and tibia total volumetric BMD by HR-pQCT.

Our Secondary endpoints:

24- hour Urine Acid Excretion at 6 months. We will examine between treatment group changes in 24-hour urinary acid excretion in potassium citrate vs. placebo groups.

Other secondary endpoints are changes in parathyroid hormone and circulating biomarkers of bone resorption (C-terminal telopeptides of type I collagen) and bone formation (procollagen type-1 N-terminal propeptide)) at 6 months. We will examine between and within group changes in bone turnover markers after 6 months of treatment with potassium citrate vs. placebo.

12.3. Data Quality

We will use a centralized **REDCap database**, as for our previous studies. REDCap is a secure data management tool that permits multi-center studies. All clinical, lab and imaging data will be entered at the relevant local institution level into REDCap, which will then be accessible to relevant study personnel.

REDCap will allow for rigorous data management, quality control and protocol monitoring. Data will be entered by coordinators into REDCap, the secure, web-based data collection and study management tool. The system provides real-time data checks at the time of entry including missing data, range checks and cross-field validation. Customizable reports for monitoring of enrollment, visit compliance, and task lists are available in real time to study investigators and coordinators. All clinical research coordinators are trained to use the system.

HR-pQCT Quality Control. We perform daily scans of a phantom containing rods of hydroxyapatite (HA) with calibrated densities (i.e., 0, 100, 200, 400, and 800 mg HA/cm³; QRM, Moehrendorf, Germany). Images will be scored for movement at acquisition using (score 1-5 with 1 indicating best quality) and repeated for scores >2. If images are scored >3 at the time of analysis, they will be excluded.

Confidentiality

A risk is the potential risk for breach of confidentiality of the subject data. Every effort will be made to keep secure subject names and addresses. All study information will be kept in locked file cabinets and on password protected computers. We will use secure REDCap database storage. Research personnel will be or have already been trained in use of REDCap. Identifiers will be excluded from any patient data analyzed and meetings with investigators.

REDCap is designed for Multi-Site Research. The REDCap database will be coded, with personal identifiers removed. A coded list will be maintained by each recruiting side in a locked file cabinet and on password protected computers. Investigators will comply with NIH regulations and data will be stored for a minimum of 7 years after publication of the trial findings. Access to the REDCap database will be limited to investigators and study coordinators. REDCap data allows data to be shared without needing to be transported. Study coordinators will be responsible for data entry, and study investigators will review the data entered at their regular meetings for data quality control.

12.4. Future Use of Data

Data will be stored in the REDCap database for a minimum of 7 years. Wherever

applicable, data will be deposited to appropriate public repositories. It will only be accessed with permission of the multiple PIs. The proposed research will generate data on urinary excretion of acid, bone biomarkers and bone imaging (HR-pQCT) in response to potassium citrate vs. placebo in children and adults with CKD. All investigators are aware of and agree to abide by the principles for sharing research resources, as described by NIH in "Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Programs." The data generated in this grant will be presented at national or international conferences and published in a timely fashion. All final peer-reviewed manuscripts that arise from this proposal will be submitted to the digital archive PubMed Central. Wherever applicable, data will be deposited to appropriate public repositories. Should any intellectual property arise which requires a patent, we would ensure that the technology remains widely available to the research community in accordance with the NIH Principles and Guidelines document.

13. PROTECTING THE PRIVACY OF SUBJECTS

Recruitment and Informed Consent. Intervention recruitment and consent will not begin until the study receives approval from the Columbia University single IRBs. We will use a searchable (by diagnosis code and lab values) electronic database of patients at Montefiore. We will obtain permission to contact the eligible patients from the primary nephrologist. A study coordinator will call them in a few days to provide information and to answer any questions. The patient will be asked about interest in participation. If they express interest, the study will be discussed with them, and they will be provided an appointment for an in-person screening visit. If they would like more time to think about participation in the study, we will provide them with the research coordinator's phone number and call them in a week's time to assess their interest. We will review the informed consent document and will perform the eligibility screening. After the screening is complete and if they qualify to join the study, the participants will be offered a choice of either having an enrollment visit in the Clinical Research Center or as part of their next regularly scheduled Nephrology appointment. Participation in the proposed study will be completely voluntary. All participants will receive remuneration for their time and to defray travel costs to the study visits. Participants will be provided with \$75 for each of the imaging in person visits, \$10 for laboratory visits outside of clinical care, and \$50 for non-imaging visits. Prospective subjects will be told that a decision to decline participation will not affect their medical care. The consent procedures will include information about study procedures, including that subjects will be randomized, which means they may be randomized to placebo. This proposed research procedure will follow the Health Insurance Portability and Accountability Act of 1996 (HIPAA) guidelines for protecting the privacy and documenting informed consent of participants.

Protection Against Risk. We will not access participants social media accounts.

All procedures will be performed to maximize participant privacy. All procedures will be performed in a private room with study technician and subject. Participants will be able to wear their own clothing during the HRpQCT imaging. Procedure will be performed with maximum respect to the subject's personal space.

14. ENSURING THE SAFETY OF SUBJECTS

Definitions and Reporting

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Adverse events may be categorized as follows: (i) Adverse reaction – any adverse event caused by the drug. (ii) Unexpected Adverse Event – An adverse event is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the application or study materials provided to Columbia University IRB. (iii) Related – An event is related to the research procedures if in the opinion of the principal investigator, it was more likely than not to be caused by the research procedures. (iv) Serious Adverse Events (SAEs) – as indicated below.

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the end of study treatment follow-up is defined as the last study visit at the end of Study Phase 2.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the

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character of the condition worsens during the study period.

Post-study Adverse Event

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any related adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Each participating investigator must report every serious adverse event (SAE) to the IND sponsor at Columbia University Irving Medical Center within 24 hours of becoming aware of the occurrence using the SAE Report Form. The site investigator must document the time of his or her awareness of the SAE and report the SAE by email or facsimile to:

Name: Thomas L. Nickolas MD MS
Tel: 212-305-9847
Fax: 212-305-4981
Email: tln2001@cumc.columbia.edu

The participating investigator must also provide follow-up information on the SAE once new or updated information is available. The follow-up information will be provided on

the SAE Report Form but should be noted as a follow-up to an initial report.

Non-serious adverse events will be reported to the IND sponsor at Columbia University Irving Medical Center on the Adverse Event Form through email or facsimile to:

Name: Thomas L. Nickolas MD MS

Tel: 212-305-9847

Fax: 212-305-4981

Email: tln2001@cumc.columbia.edu

All SAE's and non-serious adverse events will be recorded in REDCap no later than 2 weeks from the date of data collection or event awareness.

Reporting to the IRB

Serious adverse events that are both **unexpected and related** will be reported to the IRB and DSMB as soon as possible, but in no event later than 5 business days of the researcher becoming aware of the event, using the Reportable Event Form. The IND sponsor will report the applicable events to the single IRB (CUIMC) according to CUIRB policies (i.e., within 5 working days of event awareness or assessment as SAE/UP).

Unanticipated Problem (UP):

An unanticipated problem is any incident, experience or outcome involving risks to subjects or others in any human subjects' research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (e.g., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Reports of all events (including follow-up information) that meet the definition of an unanticipated problem posing risk to subjects or others must be submitted to the IRB within one week (5 business days) following the occurrence of the unanticipated problem or the investigator's acquiring knowledge of the unanticipated problem in accordance with IRB policy. Additionally, the investigator will submit a summary of all unanticipated problems that occurred since the beginning of the study at the time of continuing review.

Reporting to the FDA

Suspected Adverse Reaction:

In accordance with 21 CFR 312.32(a), a suspected adverse reaction (SAR) means any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

The IND Sponsor will be responsible for all communication with the FDA and will report to the FDA, any adverse event that is serious, unexpected and for which there is reasonable possibility that the drug caused the adverse event. These must be reported to the FDA as soon as possible, but no later than 15 calendar days after the Sponsor determines that the information qualifies for reporting. Any fatal or life-threatening

SARs will be reported to the FDA as soon as possible, but no later than 7 calendar days after the Sponsor determines that the information qualifies for such reporting.

All other serious adverse events will be included in the IND annual reports that are to be submitted to the FDA within 60 days of the anniversary date of the IND each year.

Reporting to Participating Sites

The IND Sponsor will notify all participating sites of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. In addition, the IND sponsor will review available reports concerning similar adverse events and analyze the significance of available information.

Reporting to DMSB

Study Stoppage Criteria

The DSMB will utilize predefined criteria to terminate the study in the setting of an excess of SAEs or grade 3 AEs in the active drug group relative to the placebo group. Study stoppage criteria will be defined as:

1. SAE event rates of 10% in a ratio of 2:1 in the active drug vs. placebo groups
2. Grade 3 AE rate of 20% in a ratio of 2:1 in the active drug vs. placebo groups

15. RISKS TO SUBJECTS

Potential Risks of Potassium Citrate.

We will be monitoring for signs of potential side effects of oral potassium citrate supplementation including hyperkalemia, alkalosis, gastrointestinal intolerance, tingling sensation, weakness, mental confusion, or irregular heart rhythm.

Potential Risks

Potassium Supplementation: We will be monitoring for signs of potential side effects of oral potassium supplementation including hyperkalemia, alkalosis, gastrointestinal intolerance, burning or tingling sensation, weakness, mental confusion, low blood pressure, or irregular heart rhythm.

Alkali Therapy: We will be monitoring for signs of potential side effects of oral alkali therapy including severe alkalosis and gastrointestinal intolerance.

Safety monitoring for hyperkalemia and alkalosis:

All subjects will be given a card to identify them as a part of this study. The card will provide instructions to contact the study team in the event of hyperkalemia or alkalosis.

Simultaneous venous blood gas, serum potassium, creatinine and calcium, and bicarbonate will be obtained 2-5 days after starting the treatment during the run-in phase. To enter phase 2, participants will need 2 blood tests with a serum potassium <5.5 mEq/L two weeks apart. It will also be monitored 2-5 days after starting treatment following randomization and during the study visits at 3- and 6-months.

If at any point during either phase 1 (run-in) or phase 2 (randomization) participants develop hyperkalemia ($K > 5.5$ mEq/L), the following protocol will be

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followed:

- If the serum potassium is 5.5--5.9 mEq/L or a serum bicarbonate >30 mEq/L, the dose will be decreased by 50% and participants will have repeat blood work after 2-5 days.
- If serum potassium ≥ 6.0 mEq/L, the study medication will be held, an ECG obtained, a potassium binder will be given, and potassium will be repeated within 24 hours. If potassium is improved, subjects will be given study medication at 50% of the original starting dose and blood work will be repeated after 2-5 days.
- Participants with recurrent serum potassium >5.5 mEq/L despite dose adjustment will be withdrawn from the study (phase 1) or have study drug stopped (phase 2).
- All participants who develop hyperkalemia will be referred back to their primary nephrologist to pursue a work-up and further treatment for hyperkalemia as appropriate.

If at any point during either phase 1 (run-in) or phase 2 (randomization) a participant develops alkalosis (serum bicarbonate >30 mEq/L), the following protocol will be followed:

- If the serum bicarbonate >30 mEq/L, the dose will be decreased by 50% and participants will have repeat blood work after 2-5 days.
- If the serum bicarbonate is >30 mEq/L on 2 subsequent blood draws despite dose adjustment: for phase 1, the participant will be withdrawn from the study. For phase 2, study drug will be discontinued, the participant will continue in the study and complete all study procedures.

Other potential side effects: Doses will be modified in cases of hyperkalemia and/or metabolic alkalosis. Low BP is possible due to effects of potassium on blood pressure. BPs will be measured in the run-in phase and after randomization during lab and in person follow-up visits. BP will be determined at all visits as the mean of three measurements taken at least 1 minute apart after a minimum of 5 minutes at rest in the seated position.

At any point in the study, if the potassium is ≥ 6.0 mEq/L an ECG will be obtained.

If blood pressures are high (>130/80 or >95th percentile for age/sex/height in children) or low (<100/60 in adults), the investigators will contact the primary nephrologist to adjust antihypertensive medications and/or diuretics. If participants experience significant gastrointestinal distress, the dose may be decreased by 50%.

To assess for risk of nephrolithiasis, urine pH will be monitored.

Participants will be removed from the study if the following adverse events occur:

- serum bicarbonate <18 mEq/L or >30 mEq/L twice (despite dose modification)
- potassium persistently >5.5 mEq/L despite dose adjustment
- potassium <3.5 mEq/L
- total calcium (corrected for serum albumin) <7.5 mg/dL
- serum creatinine translating to eGFR <20 ml/min per 1.73 m²
- intolerance of medication despite dose adjustment
- initiation of dialysis or transplant
- pregnancy
- ECG abnormality associated with arrhythmia (except left ventricular hypertrophy)
- urine pH >8 twice or nephrolithiasis
- an event that in the opinion of the investigator(s) requires removal from the study

Radiation

The total expected radiation dose for HR-pQCT is up to 60 μ Sv. One study (5 μ Sv for forearm, 5 μ Sv for leg) is approximately 10 μ Sv, thus it would 40 μ Sv total for the 2-sets of scans obtained at the baseline and 6-month visits. We added 20 μ Sv to cover up to two repeat scans per visit in the event of movement. This compares to 2400 μ Sv natural background in a year, 8000 μ Sv for a standard chest CT, 450 μ Sv for a mammogram, and 60 μ Sv for a round-trip transcontinental plane flight. The total radiation exposure for the study will be below the maximal acceptable dose.

Pregnancy and breastfeeding risk:

Sexually active woman of childbearing age who would like to take part of this study have to agree to use one method of birth control.

Other study procedure risks

Drawing blood, or venipuncture, may result in bruising to the arm or on rare occasions, vasovagal syncope. Where possible, blood collections will be timed with blood draws for routine clinical care.

Blood pressure measurements involve some discomfort as the sphygmomanometer is inflated.

There are no significant risks to a urine collection in toilet trained adults and children.

All these risks will be detailed in the informed consent document.

Another risk is the potential risk for breach of confidentiality of the subject data. Every effort will be made to keep secure subject names and addresses. All study information will be kept in locked file cabinets and on password protected computers. We will use secure REDCap database storage. Identifiers will be excluded from any patient data analyzed and meetings with investigators will also exclude patient identifiers.

Alternatives to this study will be explained to the potential emergency treatment participants and include continuing standard nephrology care from the subject's provider without enrollment in the trial.

Monitoring for side effects: Study coordinators will contact participants by phone monthly during both phase 1 and phase 2 to assess for symptoms and/or side effects during washout and treatment phases. Patients with new symptoms or complaints will be brought in for evaluation either in the outpatient clinic or emergency room, as appropriate.

Minimization of risks of Radiation: HR-pQCT imaging has the risk of radiation exposure. The amount of radiation that patients will receive as a result of participation in the study will be discussed with them in detail as part of informed consent process. Females will undergo a urine pregnancy test prior to the HR-pQCT imaging. Pregnant females will be excluded from the study at any time point in order to protect the unborn fetus.

Confidentiality: Every effort will be made to prevent a breach of confidentiality. All staff is trained to maintain complete confidentiality. Computerized data will be kept in password protected, encrypted files in a locked room.

Minimization of other Risks:

Experienced phlebotomists will conduct venipuncture with the patient seated. In addition, we will exclude participants who may be at higher risk of adverse events (see exclusion criteria). Provisions for ensuring necessary medical or professional intervention in the event of adverse effects will be coordinated by the site PIs at each institution.

Data and Safety Monitoring Plan:

This study is a human subjects randomized, placebo-controlled interventional clinical research trial of potassium citrate vs. placebo therapy. Potential side effects will be closely monitored for over the course of the study, including frequent lab draws to evaluate for hyperkalemia and metabolic alkalosis.

A Data Safety and Monitoring Board (DSMB) will be established to review safety and study progress. We have identified 4 researchers external to our institutions as potential members for the DSMB (letters of agreement attached). They are Dr. Tamara Isakova from Northwestern University, Dr. Farzana Perwad from the University of California at San Francisco, Dr. Derek Ng from the Johns Hopkins Bloomberg School of Public Health and Dr. Bethany Foster from the Montreal Children's Hospital. These researchers include investigators with experience in Clinical Research in Pediatric Nephrology, Internal Medicine Nephrology, skeletal imaging methods and Epidemiology/ Biostatistics. All four are not involved with the project. The DSMB will meet before the beginning of the trial enrollment and review the study protocol. They will meet every 6 months thereafter. Study recruitment, retention and protocol adherence will be reviewed by the MPI's monthly and by the DSMB every 6-months. The DSMB will review hospitalizations and any major conflicts that arise due to enrollment in the study. All adverse events will be reviewed by the MPIs and the members of the DSMB every 6-months. If there is a serious adverse event that is deemed related or possibly related to the study by one of the MPIs, a special session of the DSMB will be convened to review the event, the adjudication, and the adequacy of the remediation plan.

The DSMB will have the ability to stop the study at any point, if necessary. The MPIs will provide the DSMB with data about enrollment, adverse events, retention and protocol adherence for discussion and review during these meetings. For this purpose, all hospitalizations, lab parameters and drug reactions will be reported to the DSMB every 6 months.

Safety labs and weekly check-ins with study participants will occur according to the study timeline. These labs, as well as weekly check-ins with the participants, will be reviewed by the PIs within 24 hours of receipt of results/knowledge and will be acted upon if there are any adverse events.

Safety information will be collected via safety monitoring calls and information will be stored in the REDCap database. The PIs will review safety data including expected and unexpected adverse events, significant adverse events, and untoward events during their weekly meeting and every 6 months to the DSMB.

Adverse Event Monitoring If patients do not attend one of their appointments, they will be contacted by phone by the study coordinator. Using this method, we will be aware of any adverse events that may have occurred to the patient. Related hospital admission or death from any cause will be reported to the single IRB and the DSMB. Information about adverse events will be sought as described above. Unanticipated (non- serious) adverse events will be reported to the IRB per IRB protocols. Serious

adverse events will be reported to the IRB within 48 hours by phone, email, fax or hand delivery. All deaths will be reported to the IRB within 48 hours of ascertainment. These reports will also be sent to the Data and Safety Monitoring board at the same time as they are reported to the IRB.

WITHDRAWAL OF SUBJECTS

Participants will be removed from the study if they request to withdraw.

Phase 1, if the following adverse events occur the participants will be withdrawn:

- serum bicarbonate <18 mEq/L or >30 mEq/L twice (despite dose modification)
- potassium persistently >5.5 mEq/L despite dose adjustment
- potassium <3.5 mEq/L
- total calcium (corrected for serum albumin) <7.5 mg/dL
- serum creatinine translating to eGFR<20 ml/min per 1.73 m²
- intolerance of medication despite dose adjustment
- initiation of dialysis or transplant
- pregnancy
- ECG abnormality associated with arrhythmia (except left ventricular hypertrophy)
- urine pH >8 twice or nephrolithiasis
- an event that in the opinion of the investigator(s) requires emergency treatment

Phase 2, participants will be withdrawn from the study if they become pregnant. However, for any other criteria listed above for Phase 1, the study drug will be stopped, the patient will remain in the study and all study procedures will be completed.

The criteria for withdrawal for adult and pediatric participants will be the same.

If participant is going to withdraw from the study, they will complete a termination form and the reason for termination. We will see if they are willing to complete an end study visit before withdrawal. We will also seek their consent to continue to extract data from electronic medical records.

Because we are enrolling subjects with mild CKD, we do not anticipate that adverse events will be greater than that seen in the general healthy population. Potassium citrate is typically well tolerated, and the GI side effects are the most common adverse events. In Jehle et al. study of 89 subjects on Potassium citrate¹⁹, 2 dropouts occurred for side effects of GI discomfort and one subject reported lassitude. In a second study by Jehle et al.¹⁸ of 85 healthy subjects treated with Potassium citrate, adverse event rates were similar between those treated with placebo and Potassium citrate. The most adverse events reported were GI side effects (constipation 16.5%, diarrhea 11.8%, upper GI discomfort 3.5%, flatulence 4.7%). Less common side effect reported were pruritus (3.5%), edema (3.5%), and stronger nails (3.5%). All other reported sides effects occurred in less than 3% of subjects. No serious adverse events were reported with Potassium citrate in that study.

The majority of potential adverse effects are likely reversible with stopping the study medication, including GI discomfort and hyperkalemia.

A risk is the potential risk for breach of confidentiality of the subject data. Every effort will be made to keep secure subject names and addresses. All study information will be kept in locked file cabinets and on password protected computers. We will use secure REDCap database storage. Research personnel will be or have already been

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trained in use of REDCap. Identifiers will be excluded from any patient data analyzed and meetings with investigators.

We will keep track of other unforeseeable risks.

16. POTENTIAL BENEFITS TO SUBJECTS

The potential benefits of the proposed research involve learning more about ways to improve bone health in adult and pediatric kidney disease. The risk-benefit ratio in the proposed study is acceptable for the following reasons. First, potassium and alkali therapy have been used in adults and children for decades with low prevalence of adverse effects. The participants will not have severe kidney function impairment, and thus are less likely to have side effects from potassium supplementation. In healthy subjects, 6 months of potassium citrate supplementation improved bone density and quality, with an increase of a 1.5% increase in bone density of both the spine and hip.¹⁸ Second, we will closely monitor all participants to evaluate for side effects pro-actively. The data gathered from this clinical trial may help to provide an inexpensive intervention to improve bone health in a high-risk population, therefore provide benefit to others outside the trial.

17. SHARING OF RESULTS WITH SUBJECTS AND OTHER SITES

The data generated in this grant will be presented at national or international conferences and published in a timely fashion. All final peer-reviewed manuscripts that arise from this proposal will be submitted to the digital archive PubMed Central. Wherever applicable, data will be deposited to appropriate public repositories.

Because the HR-pQCT is research tool, we will not provide subjects with a clinical interpretation of the data. All clinical and safety labs will be provided to the subjects. All research blood assays will be performed in batches at the end of the study and results will not be provided to subjects.

Between Columbia and other Institutions

Institutions	Type of agreement	Coverage
Einstein/Montefiore	Data transfer and use agreement	For protected health Information*
Einstein/Montefiore	Material Transfer agreement	Receiving blood to process bone markers. Receiving HRpQCT files for analysis. Sending blood collected at Columbia to Einstein biorepository. Type of material: Identified.
University of Pittsburgh	Data Transfer agreement	Receive HRpQCT files for analysis. Type of data: Limited data set.
Utah University	Material Transfer agreement	Sending 24-12-hour urine samples. Type of material: Deidentified.

18. CONSENT PROCESS AND DOCUMENTATION

If a potential subject is interested in participating in the study, a study team member will consent the subject or if applicable, his/her parent/guardian at the time of recruitment in clinic or at Visit 1. Consent will be obtained either on the phone or in person. If a potential subject needs to time to consider entering the study, the coordinator will follow up in 2-4 weeks after initial contact.

Study team members will include the multi-PIs, co- investigators (Dr. Michal Melamed, Dr. Kimberly Reidy, Dr. Thomas Nickolas, Dr. Juhi Kumar, Dr. Kalani Raphael, Dr. Matthew Abramowitz, Dr. Mishaela Rubin) and study coordinators. MultiPIs and/or study coordinators will provide information about the study and obtain informed consent.

To maximize privacy, the discussion will take place in a private location. Subjects will be allowed to read the consent form and allowed to ask questions. Written consent will be obtained after all the questions and discussions have been completed, and the person obtaining consent is reassured that the subject comprehends the nature of the study, the study procedures, and the risks-benefits of participation.

The informed consent process may be performed in person as described. We anticipate it will take from 30-60 minutes to provide information about the study and obtain informed consent. Study materials and consents will be available in English and Spanish, and the study coordinators are both bilingual and fluent in Spanish. Study team will contact eligible participants via phone or on an institutionally approved HIPAA compliant electronic video conferencing platform to conduct the informed consent process remotely. The person conducting the informed consent process will carefully review each section of the informed consent form (ICF) and address the participant's or parent/guardian's questions and concerns. Once participant/ parent or guardian is ready to sign the ICF, study team will send the approved version of consent form via mail. Study team will ensure all signatures and dates are accurately documented. Any errors will be noted in a note or memo to file. Participants/ parents or guardian will be provided with a copy of the signed consent form via E-mail, fax or mail. No research-related activities will occur before the receipt of the signed ICF. To avoid coercion, the person obtaining consent will explain that study participation is voluntary and will not affect decisions made about clinical care. Decision not to participate or decision to withdraw after consent for study participation will not cause penalties or loss of any benefits otherwise entitled to the subject as a patient. In addition, the subject's current and future medical care at the site will not be affected by final decision for or against study participation.

We will use the date of birth in medical records to determine the subject's age. For subjects less than 18 years of age, consent will be obtained from one parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child. In addition, for children aged 7 to 17 years of age, written assent will be obtained by explaining briefly each method of the study while the parent/guardian is present. Informed assent will be documented on the consent form.

Medical records and referring physicians will be consulted to determine if adults can provide informed consent. Adults who are unable to provide informed consent will be excluded from the study.

Should a subject become intolerant of any aspect of the study, his/her participation (or the specific procedure) will be discontinued. A combined consent-authorization document will be used for the consent process. All subjects will be given a copy of the signed document for their records.

Intervention recruitment and consent will not begin until the study receives approval from the Columbia University single IRBs. At both the Albert Einstein College of Medicine and the University of Pittsburgh, we will use a searchable (by diagnosis code and lab values) electronic database of patients at to identify eligible patients. We will obtain permission to contact the eligible patients from the primary nephrologist. A study coordinator will call them or see them in Nephrology clinic in a few days to provide information and to answer any questions. The patient will be asked about interest in participation. If they express interest, the study will be discussed with them, and they will be provided an appointment

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for and in-person screening visit. If they would like more time to think about participation in the study, we will provide them with the research coordinator's phone number and call them in a week's time to assess their interest. If they agree to participate, they will be provided with an appointment for an in-person screening visit. We will review the informed consent document and will perform the eligibility screening. After the screening is complete and if they qualify to join the study, the participants will be offered a choice of either having an enrollment visit in the Clinical Research Center or as part of their next regularly scheduled Nephrology appointment.

Participation in the proposed study will be completely voluntary. All participants will receive remuneration for their time and to defray travel costs to the study visits. Participants will be provided with \$75 for each of the imaging in person visits, \$10 for laboratory visits outside of clinical care, and \$50 for non-imaging visits. Prospective subjects will be told that a decision to decline participation will not affect their medical care. The consent procedures will include information about study procedures, including that subjects will be randomized, which means they may be randomized to placebo. This proposed research procedure will follow the Health Insurance Portability and Accountability Act of 1996 (HIPAA) guidelines for protecting the privacy and documenting informed consent of participants.

Montefiore Medical Center

The Research Pharmacy at MMC has written policies and procedures that govern the receipt, storage, inventory process, accountability, record keeping, preparation, distribution, labeling, handling, dispensing and final disposition of study products in accordance with applicable regulations. Placebo pills and liquid will be identical and taste similar to the active comparator. The pharmacy will place the medications into capsules so that participant will receive an identical number of capsules (regardless of dose or treatment arm) so that both investigators and participants will remain blinded. Similarly, equal volumes of suspensions will be prepared for all treatment arms to maintain blinding.

Investigational Drug Services at University of Pittsburgh Medical Center (UMPC) Children's Hospital of Pittsburgh

Investigational Drug Services (IDS) is the research pharmacy for UPMC which will support the local research team with the product procurement, storage, dispensing, accountability, record keeping, labeling, handling, and final disposition of study products in accordance with applicable regulations.

Randomization will be performed by the study statistician who will stratify by center and provide the code to each research pharmacy to ensure that both pediatric centers will have equal numbers of subjects on potassium citrate and placebo.

Potassium Citrate will be supplied by:
Generic Potassium Citrate 10 mEq tablets
Mission Pharmacal Company
San Antonio, Texas, 78230 1355, USA

Generic Potassium Citrate Liquid
Pharmaceutical Associates Inc (PAI Pharma)
1700 Perimeter Road

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Greenville, SC 29605

19. DATA SAFETY AND MONITORING PLAN

This study is a human subjects randomized, placebo-controlled interventional clinical research trial of potassium citrate vs. placebo therapy. Potential side effects will be closely monitored for over the course of the study (please see Research Strategy and Protection of Human Subjects sections for details about timing of assessments), including frequent lab draws to evaluate for hyperkalemia, metabolic acidosis and metabolic alkalosis. These labs, as well as weekly check-ins with the participants at some points in the study, will be reviewed by the PIs within 24 hours and will be acted upon if there are any adverse events. The Data and Safety Monitoring Plan will address these areas as well as outline procedures for reporting adverse events that may be expected from participants >5 years old with chronic kidney disease, even though few such events are expected to be attributable to the intervention.

A Data Safety and Monitoring Board (DSMB) will be established to review safety and study progress. Four researchers external to our institutions are serving as members of the DSMB:

- Dr. Tamara Isakova, Northwestern University, Chicago IL, USA
- Dr. Farzana Perwad, University of California at San Francisco, San Francisco CA, USA
- Dr. Derek Ng, Johns Hopkins Bloomberg School of Public Health, Baltimore MD, USA
- Dr. Bethany Foster, Montreal Children's Hospital, Montreal Canada

These researchers include investigators with experience in Clinical Research in Pediatric Nephrology, Internal Medicine Nephrology, skeletal imaging methods and Epidemiology/ Biostatistics. All four are not involved with the project. The DSMB will meet before the beginning of the trial enrollment and review the study protocol. They will meet every 6 months thereafter. Study recruitment, retention and protocol adherence will be reviewed by the MPI's monthly and by the DSMB every 6-months. The DSMB will review hospitalizations and any major issues that arise due to enrollment in the study. All adverse events will be reviewed by the MPIs and the members of the DSMB every 6-months. If there is a serious adverse event that is deemed related or possibly related to the study by one of the MPIs, a special session of the DSMB will be convened to review the event, the adjudication, and the adequacy of the remediation plan. The DSMB will have the ability to stop the study at any point, if necessary. The MPIs will provide the DSMB with data about enrollment, adverse events, retention and protocol adherence for discussion and review during these meetings. For this purpose, all hospitalizations, lab parameters and drug reactions will be reported to the DSMB every 6 months.

20. TRIAL SAFETY AND MONITORING PLAN

Visit 2-3 (Run-in Phase)

For the run-in phase, all participants will receive potassium citrate. Adult participants will receive Potassium citrate (60 mEq/d, 10 mEq per tablet, three tablets twice daily). For children, we will give 1 mEq/kg/day divided into a twice a day dosing schedule. Children who cannot swallow Potassium citrate pills will be given Potassium citrate as

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a commercially available solution. For safety, a simultaneous venous blood gas pH, serum potassium, creatinine, calcium, and bicarbonate will be obtained 2-5 days after starting the medication. If the serum potassium is 5.5-5.9 mEq/L or a serum bicarbonate >30 mEq/L, the dose will be decreased by 50% and participants will have repeat blood work after 2-5 days. If the serum potassium is ≥ 6.0 mEq/L, the study medication will be held, an ECG obtained, a potassium binder will be given and serum potassium will be repeated within 24 hours. If potassium is improved, subjects will be given the study medication at 50% of the original starting dose and blood work will be repeated after 2-5 days. If the potassium is improved, we will stop the potassium binder and repeat blood work again after 2-5 days. Participants who cannot tolerate 50% of the total dose and/or with recurrent potassium >5.5 mEq/L will be withdrawn from the study. All participants who develop hyperkalemia will be referred back to their primary nephrologist to pursue a work-up and further treatment for hyperkalemia as appropriate. In addition, all participants who develop hyperkalemia will be counseled on a low potassium diet. As participants will not have severe kidney function impairment, we do not expect significant issues with hyperkalemia. In addition, alkali may lower serum potassium and prevent hyperkalemia, as was shown in Dr. Melamed's study, where 40% of participants on placebo experienced hyperkalemia (>5.0 mEq/L) compared to 19% on sodium bicarbonate. Participants will need 80% adherence to medications and 2 serum potassium levels of <5.5 mEq/L two weeks apart to enter the randomization phase. This run-in phase will determine the individualized dose (mEq of citrate) for each patient.

For safety, a simultaneous venous blood gas pH, serum potassium, creatinine, calcium, and bicarbonate and blood pressure measurement will be obtained 2-5 days after starting the medication. If the serum potassium is 5.5-5.9 mEq/L or a serum bicarbonate >30 mEq/L, the blinded dose will be decreased by 50% and participants will have repeat blood work after 2-5 days. If the serum potassium is ≥ 6.0 mEq/L, the study medication will be held, an ECG obtained, a potassium binder will be given and serum potassium will be repeated within 24 hours. If potassium is improved, subjects will be given the study medication at 50% of the original starting dose and blood work will be repeated after 2-5 days. If the potassium is improved, we will stop the potassium binder and repeat blood work again after 2-5 days. Participants who cannot tolerate 50% of the total dose and/or with recurrent potassium >5.5 mEq/L will stop the study drug but continue in the study. All participants who develop hyperkalemia will be referred back to their primary nephrologist to pursue a work-up and further treatment for hyperkalemia as appropriate. In addition, all participants who develop hyperkalemia will be counseled on a low potassium diet.

Study Stoppage Criteria:

The DSMB will utilize predefined criteria to terminate the study in the setting of an excess of SAEs or grade 3 AEs in the active drug group relative to the placebo group. Study stoppage criteria will be defined as:

- SAE event rates of 10% in a ratio of 2:1 in the active drug vs. placebo groups
- Grade 3 AE rate of 20% in a ratio of 2:1 in the active drug vs. placebo groups

Study Monitoring Activities:

This Guidance will set forth the monitoring plan for the BICARb Pilot Study will be the

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responsibility of CUIMC site primary investigator Dr. Rubin. Regular monitoring will be conducted by the QA Monitor (Monitor) of the Department of Medicine at CUIMC. The Monitor will be instructed to carry out the specific monitoring activities outlined below. Section A describes the monitoring schedule and reporting, Section B describes the data that will be reviewed on an ongoing basis and Section C describes actions to be taken in situations of non-compliance.

A. General Monitoring Schedule and Reporting

1. Pre-Study Meeting

Following development of a protocol-specific monitoring plan for each clinical study and prior to initiation of such study, the Monitor and Dr. Nickolas will meet with the lead-PI (Dr. Reidy, AECOM) and research personnel to review the study goals and study protocol requirements, including the following:

- Good Clinical Practice (GCP) requirements
- Proper delegation of authority
- Regulatory documentation
- Informed consent procedures and documentation
- Reporting requirements to the IRB
- Reporting requirements to the Sponsor, including timely submission of information for annual reports
- Procedures for enrolling subjects, including inclusion/exclusion criteria and randomization procedures (if applicable)
- Study treatment procedures
- Investigational product dispensing, administration and documentation
- Management and reporting of adverse events (AEs), serious adverse events (SAEs), unanticipated problems (UPs), deviations and violations
- Timely completion of Case Report Forms (CRFs) and appropriate source documentation

2. Scheduled Monitoring Visits

Monitoring visits will be scheduled to take place:

- After IRB approval, but prior to enrolling the first subject
- As soon as possible after the first subject is enrolled
- Every 3 months during study data collection
- After the last subject has completed his/her participation in the study.

The schedule will be reviewed and adjusted depending on the following factors:

- Rate of enrollment
- Prior history of protocol deviations or non-compliance with GCP
- Complexity of the study
- Volume of data and documentation corrections required
- Outcomes of prior monitoring visits.

3. Documentation of Findings

At the end of each monitoring visit, the Monitor will meet with the lead-PI and research personnel to review and correct any findings from the visit and discuss how to prevent similar occurrences. Within 2 weeks of each monitoring visit, a written monitoring report with the findings and required corrective actions will be issued to the lead-PI, with a copy to me. The lead-PI will be required to correct any deficiencies that do not pose immediate harm to research subjects within a month of receipt of the report. At the next

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monitoring visit, the Monitor will confirm that the deficiencies have been addressed.

The report will include, but will not be limited to, the following:

- A list of records reviewed (i.e., subject charts and medical records)
- The number of CRFs reviewed by research subject identification number and visit date
- Whether investigational product records were sufficient
- Whether there was any failure to report AEs, SAEs or Ups
- General adherence to the protocol.

B. Monitoring Specifics

Except as noted below, the Monitor and Dr. Nickolas will determine the appropriate percentage of subject files to be reviewed to obtain the information required below.

1. Qualifications of investigators and personnel

- Review CV or other documentation of qualification for each investigator and research personnel
- Verify that each CV or other documentation was current at the time of study initiation.

2. Training of investigators and research personnel

- Verify that all institutional and protocol specific training has been completed prior to study initiation, including training with respect to obtaining informed consent.

3. Delegation of authority

- Establish the identity of all research personnel who will be involved in the study
- Verify that all such personnel are listed on the Delegation of Authority Log
- Review study protocol to establish which responsibilities have been delegated
- Verify that the Delegation of Authority Log accurately reflects the delegated responsibilities and that all personnel listed have signed the log

4. Investigational Product Management

- Verify that packaging and labeling of investigational product are accurate
- Verify that investigational product has been dispensed only to eligible subjects at protocol specified doses
- Confirm that storage, dispensing, instructions for use and disposition of the investigational product comply with regulatory requirements and institutional policies
- Verify that all prescriptions were properly filled out and signed.

5. Informed consent process

- Review the Informed Consent Process Checklist for 100% of the subjects
- Verify that correct version of IRB-approved consent form was used
- Verify that each consent form was signed and dated
- Verify, by comparing the date of the consent form to the subject's medical record or other source, that the consent was signed prior to any research procedure having been performed.

6. Eligibility Criteria

- Review the Eligibility Checklists for 100% of the subjects
- Compare the protocol inclusion/exclusion criteria against each subject's medical record or other source documentation, to determine whether the subject was eligible for inclusion in the study
- Confirm that the Eligibility Checklist was signed and dated by the PI and approved by me, as Sponsor, prior to any research procedures having been performed.

7. Enrollment and screening of subjects

- Compare the number of subjects enrolled to the limit approved by the IRB
- Check subject screening and enrollment logs

8. Study procedures

- Verify that subject visits have taken place as required by the protocol
- Verify that all tests have been completed as required by the protocol
- Verify if any visit was out of allowable time parameters (out of window) by looking at subject visit schedules
- Verify any deviations by comparing the protocol with source documentation and/or subject CRFs.

9. IRB requirements

- Confirm that all protocol procedures were approved by the IRB
- Review all IRB modifications and renewals and confirm that copies of the same were delivered to me, as Sponsor
- Confirm that protocol deviations were approved by me, as Sponsor, and the IRB, unless there was a need to eliminate an immediate hazard to a subject.

10. Reporting

- Verify that AEs and SAEs have been reported to me, as Sponsor, on a timely basis
- Verify that all UPs were reported to the IRB on a timely basis
- Verify that all safety concerns, including serious unexpected suspected adverse reactions (SUSARs) that are required by FDA regulations to be reported to the FDA have been reported on a timely basis.

11. Case Report Forms and Subject Records

- Verify that the PI or his/her authorized designee has appropriately completed, signed and dated CRFs
- Verify that source documentation was used to complete CRFs
- Review data and source documents in terms of their organization, condition, completeness and legibility
- Verify that the data required by the protocol are reported accurately on the CRFs and are consistent with the source data/documents
- Verify that any dose or therapy modifications are properly documented
- Verify that AEs, SAEs, concomitant medications and underlying illnesses are reported accurately on the CRFs, in accordance with the protocol
- Verify that CRFs reflect all visits that subjects fail to make and all tests or examinations that are not performed.
- Verify that subject deaths and withdrawals and subjects lost to follow-up are reported and explained on CRFs.
- Ensure that appropriate corrections, additions or deletions are made,

dated, explained (if necessary), and initialed by the PI or his/her authorized designee.

12. Regulatory Binder

- Confirm that essential documents are included in the Regulatory Binder in accordance with the Regulatory Binder Checklist.

C. Noncompliance

1. Reporting Requirements

The lead-PI will be required to report all UPs to the IRB in accordance with institutional policies and all AEs and SAEs to me as Sponsor. I will submit reports of SUSARs to the FDA as required by 21 CFR 312.

2. Identification of Noncompliance

The Monitor will inform Dr. Nickolas immediately of the failure to report any AEs or SAEs to me or any UPs to the IRB, as well as any informed consent or protocol violations. Serious concerns that affect the safety and welfare of subjects will be dealt with by immediate action, including suspension of new enrollment or any or all research activities, as appropriate.

3. Removal of the PI(s)

If the PI(s) demonstrates that he/she cannot fulfill his/her obligations as a clinical investigator, he/she will be removed from the study and a replacement PI selected.

Reasons for removal of a PI include:

- Serious informed consent violations, such as performing research procedures prior to obtaining consent
- Major protocol violations without prior IRB approval, such as enrollment or treatment of ineligible subjects
- Delayed or lack of reporting of AEs or SAEs to me or of UPs to the IRB
- Inadequate supervision of sub-investigators and other research personnel
- Repeated delays or inadequate completion of CRFs
- Conducting research without IRB approval or during a lapse in approval.

References:

1. Nickolas TL, Leonard MB, Shane E. Chronic kidney disease and bone fracture: a growing concern. *Kidney Int.* 2008;74(6):721-31. Epub 2008/06/20. doi: 10.1038/ki.2008.264. PubMed PMID: 18563052; PMCID: PMC4139042.
2. Al-Naamani N, Maarouf OH, Ahya VN, Lederer DJ, Mendez JD, Wilt JS, Doyle AM, Rybak D, D'Ovidio F, Sonett JR, Arcasoy SM, Nickolas TL, Kawut SM. Assessment of kidney function in lung transplant candidates. *The Journal of heart and lung transplantation: the official publication of the International Society for Heart Transplantation.* 2008;27(6):635-41. doi: 10.1016/j.healun.2008.02.008. PubMed PMID: 18503963.
3. Fried LF, Biggs ML, Shlipak MG, Seliger S, Kestenbaum B, Stehman-Breen C, Sarnak M, Siscovick D, Harris T, Cauley J, Newman AB, Robbins J. Association of kidney function with incident hip fracture in older adults. *J Am Soc Nephrol.* 2007;18(1):282-6. PubMed PMID: 17167115.

4. Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, Wong C, Stehman-Breen C. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int.* 2000;58(1):396-9. doi: 10.1046/j.1523-1755.2000.00178.x. PubMed PMID: 10886587.
5. Ensrud KE, Lui LY, Taylor BC, Ishani A, Shlipak MG, Stone KL, Cauley JA, Jamal SA, Antonucci DM, Cummings SR, Osteoporotic Fractures Research G. Renal function and risk of hip and vertebral fractures in older women. *Arch Intern Med.* 2007;167(2):133-9. doi: 10.1001/archinte.167.2.133. PubMed PMID: 17242313.
6. Kim SM, Long J, Montez-Rath M, Leonard M, Chertow GM. Hip Fracture in Patients with Non-Dialysis-Requiring Chronic Kidney Disease. *J Bone Miner Res.* 2016. Epub 2016/05/05. doi: 10.1002/jbmr.2862. PubMed PMID: 27145189.
7. Denburg MR, Kumar J, Jemielita T, Brooks ER, Skversky A, Portale AA, Salusky IB, Warady BA, Furth SL, Leonard MB. Fracture Burden and Risk Factors in Childhood CKD: Results from the CKiD Cohort Study. *J Am Soc Nephrol.* 2016;27(2):543-50. Epub 2015/07/04. doi: 10.1681/asn.2015020152. PubMed PMID:26139439; PMCID: PMC4731126
8. Wesseling-Perry K, Pereira RC, Tseng CH, Elashoff R, Zaritsky JJ, Yadin O, Sahney S, Gales B, Juppner H, Salusky IB. Early skeletal and biochemical alterations in pediatric chronic kidney disease. *Clin J Am Soc Nephrol.* 2012;7(1):146-52. Epub 2011/11/05. doi: 10.2215/CJN.05940611. PubMed PMID: 22052943; PMCID: PMC3265337.
9. Wetzsteon RJ, Kalkwarf HJ, Shults J, Zemel BS, Foster BJ, Griffin L, Strife CF, Foerster DL, Jean- Pierre DK, Leonard MB. Volumetric bone mineral density and bone structure in childhood chronic kidney disease. *J Bone Miner Res.* 2011;26(9):2235-44. Epub 2011/05/19. doi: 10.1002/jbmr.427. PubMed PMID: 21590737; PMCID: PMC3304436.
10. Denburg MR, Tsampalieros AK, de Boer IH, Shults J, Kalkwarf HJ, Zemel BS, Foerster D, Stokes D, Leonard MB. Mineral metabolism and cortical volumetric bone mineral density in childhood chronic kidney disease. *The Journal of clinical endocrinology and metabolism.* 2013;98(5):1930-8. doi: 10.1210/jc.2012-4188. PubMed PMID: 23547048; PMCID: 3644604.
11. Groothoff JW, Offringa M, Van Eck-Smit BL, Gruppen MP, Van De Kar NJ, Wolff ED, Lilien MR, Davin JC, Heymans HS, Dekker FW. Severe bone disease and low bone mineral density after juvenile renal failure. *Kidney Int.* 2003;63(1):266-75. doi: 10.1046/j.1523-1755.2003.00727.x. PubMed PMID: 12472792.
12. Beaubrun AC, Kilpatrick RD, Freburger JK, Bradbury BD, Wang L, Brookhart MA. Temporal trends in fracture rates and postdischarge outcomes among hemodialysis patients. *J Am Soc Nephrol.* 2013;24(9):1461-9. doi: 10.1681/ASN.2012090916. PubMed PMID: 23744885; PMCID: 3752946.
13. Robinson DE, Ali MS, Pallares N, Tebé C, Elhussein L, Abrahamsen B, Arden NK, Ben-Shlomo Y, Caskey FJ, Cooper C, Dedman D, Delmestri A, Judge A, Pérez-Sáez MJ, Pascual J, Nogues X, Díez-Pérez A, Strauss VY, Javaid MK, Prieto-Alhambra D. Safety of oral bisphosphonates in moderate-to-severe chronic kidney disease: a bi-national cohort analysis. *J Bone Miner Res.* 2020. Epub 2020/12/30.

doi: 10.1002/jbmr.4235. PubMed PMID: 33373491

14. Ott SM. Pharmacology of Bisphosphonates in Patients with Chronic Kidney Disease. *Seminars in dialysis*. 2015;28(4):363-9. Epub 2015/05/06. doi: 10.1111/sdi.12388. PubMed PMID: 25940768.
15. Krieger NS, Sessler NE, Bushinsky DA. Acidosis inhibits osteoblastic and stimulates osteoclastic activity in vitro. *Am J Physiol*. 1992;262(3 Pt 2):F442-8. Epub 1992/03/01. doi: 10.1152/ajprenal.1992.262.3.F442. PubMed PMID: 1558161.
16. Bushinsky DA, Nilsson EL. Additive effects of acidosis and parathyroid hormone on mouse osteoblastic and osteoclastic function. *Am J Physiol*. 1995;269(6 Pt 1):C1364-70. Epub 1995/12/01. doi: 10.1152/ajp-cell.1995.269.6.C1364. PubMed PMID: 8572164.
17. Melamed ML, Horwitz EJ, Dobre MA, Abramowitz MK, Zhang L, Lo Y, Mitch WE, Hostetter TH. Effects of Sodium Bicarbonate in CKD Stages 3 and 4: A Randomized, Placebo-Controlled, Multicenter Clinical Trial. *Am J Kidney Dis*. 2020;75(2):225-34. Epub 2019/11/09. doi: 10.1053/j.ajkd.2019.07.016. PubMed PMID: 31699517; PMCID: PMC7012673.
18. Jehle S, Hulter HN, Krapf R. Effect of potassium citrate on bone density, microarchitecture, and fracture risk in healthy older adults without osteoporosis: a randomized controlled trial. *The Journal of clinical endocrinology and metabolism*. 2013;98(1):207-17. Epub 2012/11/20. doi: 10.1210/jc.2012-3099. PubMed PMID: 23162100.
19. Jehle S, Zanetti A, Muser J, Hulter HN, Krapf R. Partial neutralization of the acidogenic Western diet with potassium citrate increases bone mass in postmenopausal women with osteopenia. *J Am Soc Nephrol*. 2006;17(11):3213-22. Epub 2006/10/13. doi: 10.1681/ASN.2006030233. PubMed PMID: 17035614.
20. Lemann J, Jr., Gray RW, Pleuss JA. Potassium bicarbonate, but not sodium bicarbonate, reduces urinary calcium excretion and improves calcium balance in healthy men. *Kidney Int*. 1989;35(2):688-95. Epub 1989/02/01. doi: 10.1038/ki.1989.40. PubMed PMID: 2540373
21. Lemann J, Jr., Pleuss JA, Gray RW. Potassium causes calcium retention in healthy adults. *J Nutr*. 1993;123(9):1623-6. Epub 1993/09/01. doi: 10.1093/jn/123.9.1623. PubMed PMID: 8360791.
22. Bikbov B, Perico N, Remuzzi G, on behalf of the GBDGDEG. Disparities in Chronic Kidney Disease Prevalence among Males and Females in 195 Countries: Analysis of the Global Burden of Disease 2016 Study. *Nephron*. 2018:1-6. Epub 2018/05/24. doi: 10.1159/000489897. PubMed PMID: 29791905.
23. Nickolas TL, Stein E, Cohen A, Thomas V, Staron RB, McMahon DJ, Leonard MB, Shane E. Bone mass and microarchitecture in CKD patients with fracture. *J Am Soc Nephrol*. 2010;21(8):1371-80. Epub 2010/04/17. doi: ASN.2009121208 [pii] 10.1681/ASN.2009121208. PubMed PMID: 20395370; PMCID: PMC2938588.

24. Klawansky S, Komaroff E, Cavanaugh PF, Jr., Mitchell DY, Gordon MJ, Connelly JE, Ross SD. Relationship between age, renal function and bone mineral density in the US population. *Osteoporos Int.* 2003;14(7):570-6
doi:10.1007/s00198-003-1435-y. PubMed PMID: 2844211.
25. Johnell O. The socioeconomic burden of fractures: today and in the 21st century. *Am J Med.* 1997;103(2A):20S-5S; discussion 5S-6S. PubMed PMID: 9302894.
26. Rodig NM, McDermott KC, Schneider MF, Hotchkiss HM, Yadin O, Seikaly MG, Furth SL, Warady BA. Growth in children with chronic kidney disease: a report from the Chronic Kidney Disease in Children Study. *Pediatr Nephrol.* 2014;29(10):1987-95. Epub 2014/04/15. doi: 10.1007/s00467-014-2812-9. PubMed PMID: 24728472; PMCID: PMC4470271.
27. Sernbo I, Johnell O. Consequences of a hip fracture: a prospective study over 1 year. *Osteoporos Int.* 1993;3(3):148-53. PubMed PMID: 8481591.
28. Dooley AC, Weiss NS, Kestenbaum B. Increased risk of hip fracture among men with CKD. *Am J Kidney Dis.* 2008;51(1):38-44. PubMed PMID: 18155531.
29. Nickolas TL, McMahon DJ, Shane E. Relationship between moderate to severe kidney disease and hip fracture in the United States. *J Am Soc Nephrol.* 2006;17(11):3223-32. Epub 2006/09/29. doi: ASN.2005111194 [pii] 10.1681/ASN.2005111194. PubMed PMID: 17005938
30. Nitsch D, Mylne A, Roderick PJ, Smeeth L, Hubbard R, Fletcher A. Chronic kidney disease and hip fracture-related mortality in older people in the UK. *Nephrol Dial Transplant.* 2009;24(5):1539-44. Epub 2008/12/17. doi: gfn678 [pii] 10.1093/ndt/gfn678. PubMed PMID: 19075194.
31. Maravic M, Ostertag A, Torres PU, Cohen-Solal M. Incidence and risk factors for hip fractures in dialysis patients. *Osteoporos Int.* 2013. doi: 10.1007/s00198-013-2435-1. PubMed PMID: 23835863.
32. Ball AM, Gillen DL, Sherrard D, Weiss NS, Emerson SS, Seliger SL, Kestenbaum BR, Stehman-Breen C. Risk of hip fracture among dialysis and renal transplant recipients. *Jama.* 2002;288(23):3014-8. PubMed PMID: 12479766.
33. Naylor KL, Jamal SA, Zou G, McArthur E, Lam NN, Leslie WD, Hodsman AB, Kim SJ, Knoll GA, Fraser LA, Adachi JD, Garg AX. Fracture Incidence in Adult Kidney Transplant Recipients. *Transplantation.* 2015. doi: 10.1097/TP.0000000000000808. PubMed PMID: 26154389.
34. Denburg M, Nickolas TL. Declining Hip Fracture Rates in Dialysis Patients: Is This Winning the War? *Am J Kidney Dis.* 2018;71(2):154-6. doi: 10.1053/j.ajkd.2017.10.007. PubMed PMID: 29389383.
35. Coco M, Rush H. Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. *Am J Kidney Dis.* 2000;36(6):1115-21. Epub 2000/11/30. doi: 10.1053/ajkd.2000.19812. PubMed PMID: 11096034.
36. Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. Safety and

efficacy of risedronate in patients with age-related reduced renal function as estimated by the cockcroft and gault method: a pooled analysis of nine clinical trials. *J Bone Miner Res.* 2005;20(12):2105-15. PubMed PMID: 16294264.

37. Jamal SA, Ljunggren O, Stehman-Breen C, Cummings SR, McClung MR, Goemaere S, Ebeling PR, Franek E, Yang YC, Egbuna OI, Boonen S, Miller PD. Effects of denosumab on fracture and bone mineral density by level of kidney function. *J Bone Miner Res.* 2011;26(8):1829-35. Epub 2011/04/15. doi: 10.1002/jbmr.403. PubMed PMID: 21491487.
38. Miller PD, Schwartz EN, Chen P, Misurski DA, Krege JH. Teriparatide in postmenopausal women with osteoporosis and mild or moderate renal impairment. *Osteoporos Int.* 2007;18(1):59-68. PubMed PMID:17013567.
39. Jamal SA, Bauer DC, Ensrud KE, Cauley JA, Hochberg M, Ishani A, Cummings SR. Alendronate Treatment in Women with Normal to Severely Impaired Renal Function: An Analysis of the Fracture Intervention Trial*. *J Bone Miner Res.* 2007. PubMed PMID: 17243862.
40. Khairallah P, Nickolas TL. Bisphosphonates in Kidney Disease-Safety First. *J Bone Miner Res.* 2021. Epub 2021/04/27. doi: 10.1002/jbmr.4283. PubMed PMID: 33900635.
41. Mora Palma FJ, Ellis HA, Cook DB, Dewar JH, Ward MK, Wilkinson R, Kerr DN. Osteomalacia in patients with chronic renal failure before dialysis or transplantation. *Q J Med.* 1983;52(207):332-48. Epub 1983/01/01. PubMed PMID: 6647748.
42. Lefebvre A, de Vernejoul MC, Guerin J, Goldfarb B, Graulet AM, Morieux C. Optimal correction of acidosis changes progression of dialysis osteodystrophy. *Kidney Int.* 1989;36(6):1112-8. Epub 1989/12/01. doi: 10.1038/ki.1989.309. PubMed PMID: 2557481.
43. Ruffoni D, Fratzl P, Roschger P, Klaushofer K, Weinkamer R. The bone mineralization density distribution as a fingerprint of the mineralization process. *Bone.* 2007;40(5):1308-19. doi: 10.1016/j.bone.2007.01.012. PubMed PMID: 17337263.
44. Ruffoni D, Fratzl P, Roschger P, Phipps R, Klaushofer K, Weinkamer R. Effect of temporal changes in bone turnover on the bone mineralization density distribution: a computer simulation study. *J Bone Miner Res.* 2008;23(12):1905-14. doi: 10.1359/jbmr.080711. PubMed PMID: 18665790.
45. Roschger P, Paschalis EP, Fratzl P, Klaushofer K. Bone mineralization density distribution in health and disease. *Bone.* 2008;42(3):456-66. doi: 10.1016/j.bone.2007.10.021.
46. Furth SL, Abraham AG, Jerry-Fluker J, Schwartz GJ, Benfield M, Kaskel F, Wong C, Mak RH, Moxey-Mims M, Warady BA. Metabolic abnormalities, cardiovascular disease risk factors, and GFR decline in children with chronic kidney disease. *Clin J Am Soc Nephrol.* 2011;6(9):2132-40. Epub 2011/08/16. doi: 10.2215/CJN.07100810 CJN.07100810 [pii]. PubMed PMID: 21841064; PMCID:

3358991.

47. Lemann J, Jr., Adams ND, Wilz DR, Brenes LG. Acid and mineral balances and bone in familial proximal renal tubular acidosis. *Kidney Int.* 2000;58(3):1267-77. Epub 2000/09/06. doi: 10.1046/j.1523-1755.2000.00282.x. PubMed PMID: 10972690.
48. Fenton TR, Eliasziw M, Lyon AW, Tough SC, Hanley DA. Meta-analysis of the quantity of calcium excretion associated with the net acid excretion of the modern diet under the acid-ash diet hypothesis. *Am J Clin Nutr.* 2008;88(4):1159-66. Epub 2008/10/10. doi: 10.1093/ajcn/88.4.1159. PubMed PMID: 18842807.
49. Kurtz I, Maher T, Hulter HN, Schambelan M, Sebastian A. Effect of diet on plasma acid-base composition in normal humans. *Kidney Int.* 1983;24(5):670-80. Epub 1983/11/01. doi: 10.1038/ki.1983.210. PubMed PMID: 6663989.
50. Cordain L, Eaton SB, Sebastian A, Mann N, Lindeberg S, Watkins BA, O'Keefe JH, Brand-Miller J. Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr.* 2005;81(2):341-54. Epub 2005/02/09. doi: 10.1093/ajcn.81.2.341. PubMed PMID: 15699220.
51. Davis S, Martyn-St James M, Sanderson J, Stevens J, Goka E, Rawdin A, Sadler S, Wong R, Campbell F, Stevenson M, Strong M, Selby P, Gittoes N. A systematic review and economic evaluation of bisphosphonates for the prevention of fragility fractures. *Health technology assessment.* 2016;20(78):1-406. Epub 2016/11/02. doi: 10.3310/hta20780. PubMed PMID: 27801641; PMCID: PMC5107884.
52. Humalda JK, Yeung SMH, Geleijnse JM, Gijsbers L, Riphagen IJ, Hoorn EJ, Rotmans JI, Vogt L, Navis G, Bakker SJL, de Borst MH. Effects of Potassium or Sodium Supplementation on Mineral Homeostasis: A Controlled Dietary Intervention Study. *The Journal of clinical endocrinology and metabolism.* 2020 Sep 1;105(9):e3246-e3256. doi: 10.1210/clinem/dgaa359.
53. Khairallah P, Isakova T, Asplin J, Hamm L, Dobre M, Rahman M, Sharma K, Leonard M, Miller E, 3rd, Jaar B, Brecklin C, Yang W, Wang X, Feldman H, Wolf M, Scialla JJ. Acid Load and Phosphorus Homeostasis in CKD. *Am J Kidney Dis.* 2017;70(4):541-50. Epub 2017/06/25. doi:10.1053/j.ajkd.2017.04.022. PubMed PMID: 28645705; PMCID:PMC5804342.
54. Nickolas TL, Stein EM, Dworakowski E, Nishiyama KK, Komandah-Kosse M, Zhang CA, McMahon DJ, Liu XS, Boutroy S, Cremers S, Shane E. Rapid cortical bone loss in patients with chronic kidney disease. *J Bone Miner Res.* 2013;28(8):1811-20. doi: 10.1002/jbmr.1916. PubMed PMID: 23456850; PMCID: PMC3720694.
55. Nickolas TL, Cremers S, Zhang A, Thomas V, Stein E, Cohen A, Chauncey R, Nikkel L, Yin MT, Liu XS, Boutroy S, Staron RB, Leonard MB, McMahon DJ, Dworakowski E, Shane E. Discriminants of prevalent fractures in chronic kidney disease. *J Am Soc Nephrol.* 2011;22(8):1560-72. Epub 2011/07/26. doi: ASN.2010121275 [pii] 10.1681/ASN.2010121275. PubMed PMID: 21784896; PMCID: PMC3148711

Appendix A: RESOURCES

Albert Einstein College of Medicine/ Montefiore Medical Center

On his 74th birthday, March 15, 1953, Professor Albert Einstein formally granted the use of his name for the first medical school built in New York City since 1897. Einstein opened in 1955 as a constituent college of Yeshiva University. In addition to the medical school, Einstein is home to the Graduate School of Medical Sciences, the Belfer Institute for Advanced Biomedical Studies and the Price Center for Genetic and Translational Medicine. There are 690 research scientists and 1,986 total faculty including clinicians, educators, and research investigators at Einstein, with 724 medical students, 158 PhD students, 106 MSTP students and 265 postdocs. It is the affiliated medical school for seven of the 16 largest hospitals in New York City and operates the largest post-graduate medical training program in the United States, offering 156 residency programs to 2,600 physicians in training. Montefiore and its affiliated hospitals serve the diverse 1.4 million residents of the Bronx with a large percentage of minorities. Montefiore Health System is comprised of 11 hospitals, including the Children's Hospital at Montefiore, Burke Rehabilitation Hospital and close to 200 outpatient care sites. Einstein received \$178 million in funding from the National Institutes of Health during 2019. This includes the funding for major research centers at Einstein in aging, intellectual development disorders, diabetes, cancer, clinical and translational re- search, liver disease and AIDS. Other areas of focus include developmental brain re- search, neuroscience, cardiac disease, and initiatives to reduce and eliminate ethnic and racial health disparities. Einstein runs one of the largest residency and fellowship training programs in the medical and dental professions in the United States through Montefiore and a network of affiliates that includes hospitals and medical centers in the Bronx and Westchester, NY.

The Einstein-Montefiore collaboration includes four jointly run Centers of Excellence and is further strengthened by the dual appointments of faculty and physicians across both institutions – enhancing synergies in research, teaching and patient care. Combining nationally recognized clinical excellence with a population health perspective that focuses on the comprehensive needs of the communities it serves, Montefiore delivers coordinated, compassionate, science-driven care where, when and how patients need it most. It is well known that the success of Einstein's research programs derives in large part from synergistic interdisciplinary collaborations, and this has been exemplified in kidney research (see below). Traditional barriers between departments and specialized facilities have been eliminated by creation of Centers and shared facilities that provide an interactive environment that fosters joint efforts among basic scientists, clinicians, behavioral scientists, and translational researchers. In addition to the Stem Cell Research a number of relevant Centers and interdisciplinary pro- grams exist including: the Albert Einstein Cancer Center (NCI; AECC), the Institute for Clinical and Translational Research, which serves as the home of the Einstein Clinical and Translational Science Award (CTSA), the Einstein-Mount Sinai Diabetes Re- search Center (NIDDK), New Your Regional Center for Diabetes Translation Re- search, the New York Obesity Center in collaboration with Columbia University, the Liver Research Center (NIDDK), the Human Genetics Program, the NIAID Center for AIDS Research, the Rose Fitzgerald Kennedy Center for Research in Mental Retar- dation and Human Development, and the Bronx Center to Reduce and Eliminate Health Disparities. Housed in the Price Center building, the Michael F. Price Center for Genetic and Translational Medicine/ Harold and Muriel Block Research Pavilion expands research endeavors focused on interactions between genetic and environ- mental factors. It houses 40 state-of-the-art laboratories in addition to research support facilities and a 100-seat auditorium.

Montefiore Health System: Montefiore Health System (MHS) is a premier academic health system, serving 2.4 million people in the Bronx and Westchester. MHS is the largest employer in the Bronx. MHS is now comprised of 11 hospitals, a rehabilitation hospital, a campus with an advanced treatment “hospital without beds”, a multi-county ambulatory network, a skilled nursing facility, a School of Nursing, a home health agency and NY State’s first freestanding emergency room. Comprised of four hospitals with 1,491 beds, Montefiore has 93,000 annual hospital admissions. Connected by a robust health information technology system (HIT), Montefiore provides more than 2.6 million ambulatory visits through a network of nearly 100 locations - from community-based ambulatory care centers to school-based health centers to mobile clinics. With nearly 300,000 visits per year, Montefiore's emergency department is one of the busiest in the nation, while the home health program provides over 500,000 visits annually. Forty percent of revenues from inpatient discharges stem from Medicare, 37 percent from Medicaid and 23 percent from commercial and other insurance. Montefiore's approach has yielded a financially stable and flourishing organization that produces high-quality outcomes. Montefiore has also created a strong alignment with its practicing physicians-more than 1,600 of whom are employed by the medical center-to provide high-quality, cost-effective care; promote community health; and improve patient outcomes. The comprehensive primary care sites are certified Level 3 Patient-Centered Medical Homes – providing team-based, patient-centered care that strengthens the doctor-patient relationship.

Children’s Hospital at Montefiore. The Department of Pediatrics is located in a new, state of the art Children’s Hospital with 130 beds. The grant support for the Department of Pediatrics has doubled in the last 2 years, reaching a level of approximately 20 million dollars in 2015. CHAM. has been recognized by U.S. News & World Report as one of the best in the nation for the fourth consecutive year. Our pediatric nephrology program ranks among the top 25 nationally.

Department of Medicine: Division of Nephrology. Dr. Abramowitz is a member of the Division of Nephrology in the Department of Medicine at the Albert Einstein College of Medicine. The Division is led by Dr. Michael Ross who is an R01-funded investigator and leader in HIV and kidney disease research. There are currently 26 full-time members of the Division who are conducting research on a variety of clinical and basic investigations including: the role of vitamin D and omega-3 fatty acids in kidney disease, the pathobiology of HIV infection in the kidney, the role of gender in kidney disease, the effects of a peer mentorship intervention in patients receiving hemodialysis, transplant outcomes and APOL1, and other research projects. NIH funding in the Division totals almost \$2,000,000 yearly. The Division also shares a T32 NIH training grant with the Division of Pediatric Nephrology. The Division holds weekly research meetings, journal clubs and renal grand rounds. The Division has been ranked in the top 50 Divisions of Nephrology nationally by U.S. News & World Report.

The Division of Pediatric Nephrology. Dr. Reidy is the Chief of the Division of Pediatric Nephrology. The Ira Greifer Children's Kidney Center at CHAM is a state-of-the-art facility dedicated to providing family-centered comprehensive care to pediatric patients with kidney problems from birth to adulthood. The Children's Kidney Center, established in 1966, one of the foremost institutions of its kind nation- and world-wide, is recognized for excellence in the evaluation, diagnosis, and treatment of pediatric kidney disorders. The Dialysis and Transplantation services, started in 1972, is where one of the first kidney transplants in a child was performed. Currently, approximately 2000 patients are seen yearly in the outpatient pediatric nephrology faculty practice,

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15 children are on maintenance dialysis, and 8-12 pediatric patients receive kidney transplants each year. A multi-disciplinary team with expertise in all aspects of nephrologic, urologic and transplantation medicine offers children with renal disease and their families the best possible care in an atmosphere of compassionate, family-centered concern. Recognition by parents and a broad referral base generate a large group of patients with a variety of renal disorders. That ensures the training of our fellows and serves as a source for clinical research projects.

There are several on-going multi-center trials sponsored by NIH-NIDDK and the Council of Pediatric Nephrology/Urology of the Kidney and Urologic Foundation of America. NIH funded studies include a multicenter therapeutic trial FSGS, a study of chronic kidney disease in children (CKiD), and The Nephrotic Syndrome Study Network (NEPTUNE), part of NIH Rare Diseases Clinical Research Network (RDCRN).

Clinical Research Center: The CRC is dedicated to patient-oriented research. The main purpose of the CRC is to provide investigators with infrastructure for studies of normal and abnormal body function and for investigation of the cause, progression, prevention, control and cure of human disease. The West Campus CRC is located on the fourth floor of the Moses Research Pavilion in proximity to the Children's Hospital at Montefiore (CHAM) and the Greene Medical Arts Pavilion (MAP) at the Montefiore Medical Center. This 2,300 sq. ft. state-of-the-art facility is the product of a clinical research partnership between Montefiore and the Albert Einstein College of Medicine and includes five exam/consult rooms, administrative offices, a conference room, reception and waiting room areas, and a sample processing laboratory. There are forty active studies taking place at the West Campus facility including twenty-one Pediatric translational research protocols. Resources include specialized nursing staff, outpatient and in-patient access and support for intensive studies involving adults and children. The latter are conducted in a procedure unit within the hospital designed for infusion studies, biopsies, and exercise experiments. Montefiore Medical Center (MMC) has operational oversight of this outpatient facility, and the CRC is under MMC's JCAHO accreditation. Ancillary laboratory tests are performed by the Department of Pathology at Montefiore at Department of Health and Human Services (DHHS)-negotiated discounts.

The Research Pharmacy at MMC has written policies and procedures that govern the receipt, storage, inventory process, accountability, record keeping, preparation, distribution, labeling, handling, dispensing and final disposition of study products in accordance with applicable regulations. All physicians who use the CRC are on the medical staff of MMC as well as on the Einstein faculty. Ongoing interactions between investigators and the CRC patient care staff are encouraged. Early on in the process of protocol development, the CRC Clinical Staff Director is involved in discussion of any protocol that includes CRC use. Concurrent with IRB review, all protocols that make use of the CRC are reviewed by the Protocol Review Committee (PRC). Multi-center clinical trials, both industry- and NIH sponsored now undergo a streamlined review process in this committee. Following the PRC review, the Clinical Staff Director discusses the logistics of protocol implementation with the Program and Executive Directors. Initiation of the protocol requires that the PI and staff consider various implementation issues, including the training of the CRC staff in study procedures.

The Einstein Library: In addition to the most of 1,200 full text online journals accessible through the school network, the Gottesman library, located in the first three floors of our building complex contains a collection of approximately 200,000 volumes and 2,000 currently received print journal titles. Electronic access to many databases and resources such as: MEDLINE, Web of Science, Faculty of 1000, is also provided on

line through the library.

Shared Facilities and NIH funded Cores, Centers and Institutes. Einstein supports a broad array of Shared Scientific Facilities and Cores designed to advance the research efforts of Einstein investigators. These Shared Facilities and Cores are operated by experienced personnel to provide researchers with access to a wide array of techniques and services requiring expensive instrumentation, specialized facilities and/or a high degree of expertise to perform. They are administered by various Einstein Centers and Departments. To facilitate rapid access to these technologies, Shared Facilities and Cores maintain web sites describing the services they provide and how to access them. Links to these sites are grouped based on the research activities supported by the Shared Facilities and Cores. For many years, Einstein has operated multiple Core facilities that are available to all faculty members and their trainees. User fees at these shared facilities are heavily subsidized by six of the eight NIH-sponsored Centers at Einstein. Each of the common facilities is directed by a full-time faculty member who is an expert in the specific area. The Director is available to trainees for consultation prior to and during a project. In addition, a senior technician is responsible for the operation and maintenance of each facility. Thus, facilities serve both to provide services and as sources of scientific training and consultation. Investigators whose work involves extensive use of a facility are encouraged to become familiar with the experimental procedures and equipment and, in many cases, to carry out the experimental protocols themselves. The supervision provided by the experienced technical staff and faculty accelerates the acquisition of expertise and ensures quality control. On the other hand, facilities can provide a service function to those scientists whose work requires only occasional Core services. The Institutional facilities provide services to faculty through a charge back system. Core facilities receive Institutional support from Einstein since the charge back costs for use of each of these facilities does not cover actual costs. Investigators can take advantage of the cost-effective use of institutionally subsidized facilities and those specifically funded by the relevant Centers.

The following facilities and institutes are available:

Harold and Muriel Block Institute for Clinical and Translational Research: The Einstein-Montefiore Institute for Clinical and Translational Research (ICTR) serves as the home of our CTSA program. NCATS-funded CTSA (UL1 TR001073, TL1 TR001072, and KL2 TR001071) The Albert Einstein College of Medicine and Montefiore Medical Center were awarded a Clinical and Translational Science Award (CTSA) by NIH in 2008, which supports the Harold and Muriel Block Institute for Clinical and Translational Research at Einstein and Montefiore (ICTR). The CTSA is a national consortium that links 60 institutions. The Consortium provides an academic home for clinical and translational science. The ICTR has status as an academic entity with committed space and resources, to advance clinical and translational research (CTR), and has authority to sponsor a PhD in clinical investigation and other training and career development programs.

The goals of the ICTR are:

- 1) To provide integrated resources and services to support and expedite planning, implementation, and completion of CTR across the entire range of research;
- 2) To enhance quality, safety, and efficiency of CTR for all diseases and conditions in our institutions;
- 3) To develop new innovations that advance clinical and translational sciences;
- 4) To facilitate the training and career development of a robust translational research

workforce.

The ICTR's core services include the: 1) Clinical Trials and Regulatory Support Office; 2) Clinical Investigation Services Cores; 3) Biostatistics, Epidemiology & Research Design; 4) Biomarker and Analytic Research Core; 5) Biospecimen Repository; 6) Community Engagement Consultation Core; 7) Research Informatics Core; and 8) Project Acceleration Resource. The ICTR and Einstein's Research Training, Education and Career Development program creates an educational environment with a learner-centered approach focused on the core competencies developed by the CTSA. These include providing a menu of options to serve learners at various stages of development across the spectrum of clinical and translational research; implementing novel mentoring approaches to foster learning communities; and supporting interdisciplinary collaboration through emphasis on methods that promote a team-based approach to scientific inquiry.

The ICTR can provide consultation including advanced statistical support for data analyses and language translation of project materials. Dr. Yungtai Lo, as faculty in the Division of Biostatistics in the Department of Epidemiology and Population Health, is part of the team that provides this statistical and epidemiologic support for clinical and translational research projects. The ICTR mission is to enhance the discipline of clinical and translational research by promoting multidisciplinary collaboration, addressing translational 'blocks' in research, providing infrastructure and collaborative support, and enhancing training, education, and career development.

Computing: Einstein maintains a sophisticated computing network staffed by highly qualified personnel who are available to assist and train students, postdoctoral fellows and faculty members. Every laboratory has multiple computers available. In addition, four large computing rooms on campus contain multiple PC and Macintosh computers. Each of these computers is hardwired to the Einstein network (ALNET) providing connections to the central Einstein computers and the internet, allowing trainees and faculty to access scientific software (e.g., graphics, statistical packages, sequence analysis software, etc.), DNA and protein databases, bibliographic data- bases from Einstein or remote locations. In addition, Einstein recently implemented a new, faster and more secure wireless network accessible from any location on campus. The fully computerized library contains an outstanding collection of 2433 scientific journals ranging from medicine to biology to chemistry to physics and can be accessed from any workstation within the university or from home. Einstein has also established a new Department for Informational Technology that reaches out to scientists to meet IT needs. Large investments by the Medical Center have resulted in a comprehensive medical information system and electronic medical records, including orders and prescriptions, with robust utilities that aggregate and anonymize data that are then available for use by clinical researchers. The new Research Informatics Core (see below for more information) aggregates substantial assets and Institutional resources such as the extensive databases and tools developed by the Montefiore Medical Center medical information system and the Einstein Bioinformatics Shared Resource. This Core will be a virtual data warehouse through which clinical and scientific data can be assembled and amalgamated.

Research Informatics Core (RIC) of the ICTR: The Research Informatics Core provides essential computational and data management support to clinical, translational and basic science researchers. Its mission is to facilitate the study and understanding of biological processes, diseases, and the relationships among them using techniques

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to derive meaning from raw experimental data. The staff of bioinformaticians, database experts and programmers possess a unique set of skills to ensure proper analysis of research needs and development of well-designed data management systems and analytic tools. Direct collaboration and consultation with investigators in research and database design. Services include the following: Transfer, secure storage, and processing of large quantities of experimental data; Provision and support of a software “toolchest” for data capture, retrieval and analysis; Support for biospecimen annotation and linkage with clinical data; Development of tools for integration of data from disparate sources; Development and maintenance of clinical research management systems; and assurance of data conformance to national standards to facilitate intra- and extramural collaboration. We will use the Research Informatics Core to assist with data management using REDCap for the BICARb trial.

Biorepository: The biorepository was established in 2007 to serve for the human research blood and tissue storage needs of the clinical and translational research community. The Core is directed by Dr. Daniel Stein and oversees the procurement of malignant, benign, diseased and uninvolved (normal) tissues from both solid and hematological malignancies, and is supported by several Institutional initiatives, including a universal opt-in consent process in use at Montefiore Medical Center, dedicated staffing for tissue acquisition in cooperation with Surgical Pathology, Clinical Research Informatics support linking samples to medical and research records, and dedicated secure storage space utilizing the most advanced, energy efficient freezer technology. A web-based application has been developed that allows investigators to determine the availability of tissue in the biorepository with necessary phenotypic characteristics for their studies. Sample types include fresh and frozen tissues, blood, urine, other biofluids and FFPE (formalin fixed, paraffin embedded) slides. The biorepository currently houses 195,000 samples, representing 45% of all biorepository samples. The biorepository services encompass patient informed consent at initial cancer evaluation, centralized management of specimen collection, processing and storage, and multiple levels of security and protection of the resource, including a Wifi-enabled NIST-calibrated temperature monitoring system has been installed on each biorepository freezer as a backup to the institutional alarm monitoring. This provides 24/7 temperature monitoring and logging and is accessible by biorepository staff remotely. The monitoring system is FDA 21CFR11-compliant for sponsored research studies. The biorepository utilizes highly-energy and space-efficient -80 C freezer technology from Global Cooling, LLC that use Stirling cooling engines that have a strong record of durability and reliability in the aerospace industry, ensuring that high-value samples are secure. These freezers use 1/3rd the amount of energy of equivalent freezers, and store 20% more samples in the same physical footprint compared to conventional freezers. This has allowed the biorepository to grow in capacity without exceeding the emergency backup diesel generator power supply available. This system activated flawlessly during recent power outages and brownouts. All conventional freezers are planned for replacement with this technology. Broad based Institutional consent for the storage and future use of leftover tissue and biofluid samples was developed and approved. Samples are distributed to investigators based upon protocol requirements, availability and merit, and distribution is prioritized accordingly. Prior to the release of any biospecimens, the staff confirm that any proposed use is consistent with an IRB- approved protocol. Mechanisms for requested collaborations from outside investigators for use of banked tissues have been established. All samples provided to outside collaborators are verified to have had appropriate broad consent from the patient donors. Ongoing Institutional initiatives include further dissemination of the universal “opt-in” consent procedures, and

automating linkage of patient medical and health information that is annotated to the biospecimens. We will use the biorepository to store samples for the proposed BICARb Trial.

Laboratory: The Biomarker Analytic Research Core (BARC) currently supports investigators at all stages from planning through implementation of sample acquisition, preservation, secure chain of custody with bar codes, quality analysis and secure data output. Specific services provided to all investigators include 1) Routine processing and storage, 2) barcoding of specimens using local or sponsor provided labels, 3) secure storage on temporary basis until analyzed, shipped to external or internal research labs, or long term as part of prospective collection within the ICTR Biorepository, 4) shipping/packaging service including internationally, 5) specialty collection tube preparation, 6) specialty processing of samples including procedures for PMBC isolation, DNA pre-extraction, 7) courier transport between Einstein/Montefiore campuses and Einstein lab facilities. All samples processed are labeled with barcoded cryolabels for easy identification, and records of samples processed are trackable via the Research Database for the ICTR. Samples are stored in the Einstein Biorepository (see above). The BARC laboratory or the Montefiore Core lab (depending on the analyte) will measure clinical analytes for the proposed BICARb Trial.

Individual Investigator Resources:

Office: Dr. Matthew Abramowitz has approximately 150 square feet of office space in the Block Building on the Einstein campus. It also includes a 250 sq. ft office for the research coordinators, including Mr. Jordan Nacimba, the proposed coordinator for the current study, and post-doctoral fellows in the Division. The coordinator room houses 6 networked workstations with telephones, hanging file cabinets and storage space for Manuals of Operations and other important paperwork. Also on the second floor of the Block building is a newly renovated conference room for up to 10 people with up-to-date audio-visual equipment. This equipment has full capability to lead zoom meetings as required.

Dr. Kimberly Reidy is located at the Division of Pediatric Nephrology Office across the street from both the Hospital and the Clinical Research Center (CRC). Seven offices are equipped with up-to-date computers, printers, scanners and wireless internet services all linked to the central IT Department at Montefiore. The administrative offices provide ample space for six full-time faculty, a Nurse Coordinator, two Administrative Assistants, and six post-doctoral Fellows in Pediatric Nephrology. In addition, Dr. Reidy has office space (94 sq ft) in the Ullmann Building. The office space is complete with desk and filing space. Administrative support and pre and post award grant support is provided through the Pediatrics Department and Pediatric Nephrology Division. Dr. Yungtai Lo is located in the Division of Biostatistics in the Department of Epidemiology on the Einstein Campus. His office is in the Block building and is fully equipped with a computer for statistical analysis.

Computer: Einstein maintains a sophisticated computing network staffed by highly qualified personnel able to assist and train students, postdoctoral fellows and faculty. MPIs are equipped with Mac Pro, iMac or Dell computers. The computers are network-accessed via Ethernet and wireless service to the central Einstein server. Offices are equipped with backup storage drives, a scanner and printers. All computers are fully loaded with standard software for word processing, statistical analysis, image analysis, spread sheet and database, presentation software, Endnote, and data analysis.

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Pubmed, E-mail and Internet connections are active for all computers. The college offers DropBox service with unlimited storage in the cloud.

Columbia University Irving Medical Center (CUIMC)

Environment: The campus and multi-disciplinary research center is situated on a 20-acre campus in Northern Manhattan and accounting for roughly half of Columbia University's nearly \$3 billion annual budget, Columbia University Irving Medical Center (CUIMC) provides global leadership in scientific research, health and medical education, and patient care. CUIMC's major teaching hospital affiliates are the New York- Presbyterian Hospital and the New York State Psychiatric Institute, both of which share the CUIMC campus. The medical center also has academic affiliations with Bassett Healthcare, in Cooperstown, NY; the Isabella Geriatric Center, in New York City; and Arnot Ogden Medical Center, in Elmira, NY; and Stamford Hospital in Stamford, CT. Columbia's faculty practice is Columbia Doctors. The College of Physicians & Surgeons (P&S), founded in 1767, was the first American school to award the MD degree in 1770, and its legacy of innovation continues. Major curriculum changes implemented in 2009 reflect the changing practice of medicine in the 21st century. The Bassett Track trains students for primary care work in rural environments. P&S is one of the most research-intensive medical schools, and its students' MCAT scores and grade-point averages are among the highest in the country. Mailman School of Public Health, founded in 1922, has programs in more than 100 countries and is a leader in HIV/AIDS, public mental health, environmental health, global health, and urban health. Nearly 40 percent of Mailman's full-time faculty hold joint or interdisciplinary appointments in other Columbia University departments, schools, and centers. The school's 20 research centers include the International Center for AIDS Care and Treatment, the Center for Infection and Immunity, and the National Center for Disaster Preparedness. CUIMC consistently has been praised for the quality, innovation, and academic rigor of its educational programs, as well as for the unsurpassed excellence of its faculty. Home to approximately 4,089 students and over 3,000 part-time and full-time faculty members, the Health Sciences campus includes the four professional schools, as well as the biomedical sciences programs of the Graduate School of Arts and Sciences. Faculty members from its four schools carry out the school's core mission of educating and training future generations of health care professionals; conduct basic research with the ultimate goal of translating discoveries into new techniques for fighting disease and improving health; are responsible for a number of significant clinical breakthroughs — among them, the first blood test for cancer, the first medical use of the laser, and the first successful transfer of genes from one cell to another.

CUIMC's tradition of innovation has led to significant achievements, including the first successful heart transplant in a child; Nobel-winning developments in cardiac catheterization, isolation of the first known odor receptors in the nose, and discoveries about how memory is stored in the brain; the first use of Dilantin to treat epilepsy; development of the antibiotic bacitracin; creation of the Apgar score to assess newborns; identification of cystic fibrosis; and design of the first significant programs to reduce maternal mortality in resource-poor countries. CUIMC is especially proud of its relationship with the surrounding Washington Heights community, many of whose members have roots in the Dominican Republic and other Spanish-speaking countries. CUIMC's Office of Government and Community Affairs serves as the primary liaison between the Medical Center and the community. Currently, CUIMC has numerous research and clinical programs in Northern Manhattan, including Harlem, Washington Heights, and Inwood. The Medical Center is also the site of Core Labs and facilities with expert staff available for consult and assistance in a wide range of specialties.

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Columbia University Irving Medical Center has more than 40 state-of-the-art shared research facilities physically housed in and administered by its departments, centers, and institutes. Clinical research faculty, basic scientists, and students all benefit from the shared access to and cost of these facilities. These resources offer the highest-quality scientific technology to the community. Many of these facilities also offer education and training, as needed. The Augustus Long Health Sciences Library is one of over 25 library collections in the Columbia University Libraries system with over 500,000 total paper and electronic volumes, subscriptions to over 4,000 serials and 3,500 audio-visual, is the most complete library of any medical school in New York. Several hundred IBM- and MacIntosh workstations are available for use in its Media & Microcomputer Center. Bibliographic databases supported by the Library include MEDLINE, HEALTH, CINAHL, PsychLit, and POPLINE. Most journals are available on line.

The Department of Medicine: The Department of Medicine, in the College of Physicians and Surgeons, is the largest department in the University with over 700 faculty members. The Department is comprised of all eight of the canonical Divisions of Internal Medicine: Cardiology, Pulmonary, Gastroenterology, Nephrology, Rheumatology Endocrinology, Infectious Diseases, and Hematology & Oncology; as well as divisions focused on General Medicine, Geriatrics, Atherosclerosis, Obesity & Lipid metabolism and Experimental Therapeutics and centers focused on Translational Immunology and Human Development & Stem Cell Biology. The Medicine department faculty members are responsible for over 50% of the teaching at Columbia Physicians & Surgeons. The department of Medicine faculty members are also actively involved with the Columbia CTSA, and faculty members compose nearly half of the executive committee of the CTSA. The Department of Medicine have faculty jointly appointed with every basic science department at the Medical Center. The department has a long history of successful recruitment of for clinical trials and observational studies across every specialty. Notable studies include the ACCORD trial of intensive blood pressure and lipid lowering therapy in diabetes, the Multiethnic Study of Atherosclerosis (MESA) observational study, the HIV trials network and the CureGN study observational study of glomerular diseases. Outpatient visits are coordinate via Columbia Doctors, the faculty practice organization of Columbia which operates at the CUIMC campus and also has offices midtown Manhattan. Medicine also has 53 affiliated multispecialty practices in New York City, Rockland and Westchester counties.

The Division of Nephrology: The department has long-standing strengths in patient oriented (clinical) and basic science research and education. The Division currently counts 26 faculty members of whom twelve are engaged in basic or patient-oriented research. Seven faculty members have R01 funded programs, three faculty members have received the American Society of Nephrology Career Development Award, one faculty member is an HHMI investigator and member of the US National Academy of Sciences, three other faculty members have received independent career awards and have R01 funding. Recent graduates of our renal fellowship program are funded by K-23 and various internal pilot awards. Six Nephrology faculty members have either completed a formal curriculum in Patient Oriented Research through the Columbia CTSA or hold a Masters degree in Epidemiology or Public Health. The division has a T32 training program in Precision Nephrology and supports three centers: The Center for Glomerular Diseases, The Transplant Center and The O'Brien Urology Center.

Bone Biomarker Laboratory: is part of the Biomarkers Core Laboratory (BCL) at the Irving Institute for Clinical and Translational Research is an advanced analytical re-

source center offering research support to pre-clinical, clinical, and translational investigators at the CUIMC and other academic institutions. The 3,000 square-foot laboratory is located on the tenth floor of the Presbyterian Hospital (PH) building, adjacent to the outpatient and inpatient clinical research units of the Irving Institute. Its mission is to offer expertise as well as state-of-the-art technologies and instrumentation for the quantitative assessment of biomarkers, drugs, targeted metabolomics, and lipidomics to support clinical and translational research and pharmacokinetic studies. They develop well-validated and customized mass spectrometry-based bioanalytical assays to meet the needs of the Columbia University research community. The BCL assists investigators in identifying cost-effective and efficient analytical strategies and technology platforms to accomplish individual project end-goals. They are committed to sharing their resources and expertise and to provide assistance with all stages of experimental design, from sample collection to data analysis.

The Metabolic Bone Diseases Program (MBDP) within the Division of Endocrinology is located on the 9th floor of the Harkness Pavilion Building. There are four rooms for outpatient clinical use. Four dual energy absorptiometry (DXA) units are each housed in their own room with computer stations and automatic download functions to those who read the scans. A second-generation high resolution peripheral QCT instrument (HR-pQCT, XtremeCT2, XCT II, SCANCO Medical AG, Brüttisellen, Switzerland) is also located in the same facility.

University of Pittsburgh Medical Center (UPMC) Children's Hospital of Pittsburgh

The Children's Hospital of Pittsburgh is among the nation's leading children's hospitals. It provides state-of-the-art clinical care and houses outstanding programs in laboratory-based and patient-oriented research. The University of Pittsburgh is one of the oldest universities in the country with substantial strengths in the basic and clinical sciences. The University of Pittsburgh fosters an open, interactive environment between departments and encourages collaborative research programs.

Rangos Research Center: The Rangos Research Center (RRC), located on the 10-acre Children's Hospital of Pittsburgh campus, is comprised of 10 floors and 300,000 square feet of open laboratories with seven floors dedicated to biomedical research. The facility supports a wide variety of research activities, with emphasis areas in cancer, diabetes, genomics, heart disease, immunology, liver failure, infectious and inflammatory disease, and neuroscience. The RRC uses an open laboratory concept designed for optimal collaboration between investigators and shared use of resources. Each laboratory bay consists of ~ 900 square feet including tissue culture, fume hood, and equipment alcoves. The RRC also provides dark rooms, environmental rooms, an equipment corridor on each floor, faculty offices, and conference facilities. The flexible laboratory space can accommodate 70 principal investigators.

Office: The office of Dr. Kumar is in the building connected to the clinical area. The division has two dedicated administrative assistants, social worker and two clinical nurses. All personnel are seated in the administrative area of the facility, adjacent to clinical area. This administrative space is equipped with computer, copier, fax machine, printers and locked storage space. The office is well equipped with computer workstations that are connected to the institution network and locked file cabinet for secure storage of study related documents. The Department of Pediatrics has an internal server that is backed up each day. The PI maintains secure folders that are saved in the system for all research generated data.

The Pediatric Clinical and Translational Research Center (PCTRC): Located in Children's Hospital of Pittsburgh, the PCTRC is funded by the NIH and devoted to investigating childhood diseases in a controlled environment. The PCTRC at the UPMC Children's Hospital of Pittsburgh gives clinical investigators the tools, staffing and re- search expertise to help complete their research throughout the hospital. We help drive medical innovation and serve our patients with a friendly, comfortable space where they can take part in studies. Our facility is dedicated solely to performing re- search procedures and implementing research protocols. The PCTRC outpatient unit consists of a 2,268 square foot patient care unit located on the Lawrenceville campus. The PCTRC is located on Floor 3 of the Administrative Office Building at Children's Hospital of Pittsburgh of UPMC, accessible via the pedestrian bridge from Floor 3 of the main hospital building. The unit has a patient waiting room, four outpatient exam/testing rooms with workstations for visiting study teams and a private patient restroom. The PCTRC has iPads available to the patients for use during their visit. The PCTRC unit has a dedicated phlebotomy space, a utility room for medication preparation and dispensing, including a medication refrigerator. There is an equipment room, administrative offices, and PCTRC nursing offices. All are adjacent to each other markedly enhancing efficiency and smooth functioning of the PCTRC unit.

The PCTRC staff perform specialized nursing and testing services

- Accurate protocol implementation
- Anthropometric measurements
- IV placement and Mediport access
- Medication Administration
- Observational studies
- Patient/family education
- Point of Care HbA1C testing, Glucometer, Hemocue, hCG, Urine dip
- Serial Vital Sign monitoring
- Specimen collection, processing, and shipping (IATA certified)

The PCTRC facility includes:

- (-20) specimen freezer
- (-80) specimen freezers
- Blood pressure monitors, automated
- Central temperature monitoring (MobileView/AeroScout) is 24 hours per day, 7 days per week
- Centrifuge and microfuge: refrigerated and ambient
- Digital infant scale • Digital stadiometer • Digital standing scale
- Ice Machine for specimens
- Language translation services
- Medication refrigerator
- Specimen storage refrigerators
- YSI 2300 STAT PLUS Glucose & L-Lactate Analyzer • YSI 2500 STAT PLUS Glucose & L-Lactate Analyzer

High Resolution peripheral computed tomography (HR-pQCT): HR-pQCT will be performed at the Neuromuscular Research Laboratory within the Department of Sports Medicine and Nutrition in the School of Health and Rehabilitation Sciences.

THE UNIVERSITY OF UTAH

The University of Utah is ranked among the top 30 public research universities in the nation, is the leading research institution in the Intermountain West, and is recognized as a Tier 1 Research Institution by the Carnegie Foundation. The University promotes high academic standards and professional practice, while fostering creativity and diversity. In fiscal year 2022, the University of Utah received \$686 million in research funding from external sources (69% from federal sources) and ranks 15th in the nation for significant awards to faculty for research efforts. In 2019, the University of Utah joined the American Association of Universities, an association of 65 universities leading comprehensive research and graduate education.

University of Utah Health is the Intermountain West's only academic health care system, combining excellence in patient care with research and education. University of Utah Health consists of five hospitals and 12 community health centers and serves patients throughout the intermountain region including Utah, Nevada, Colorado, Idaho, New Mexico, Wyoming, and Montana. In addition to providing primary care and multispecialty clinical services, a major focus of the institution is education. University of Utah Health anchors allied health science graduate schools, which include the School of Medicine, College of Nursing, College of Health, College of Pharmacy, and School of Dentistry. University of Utah Health is a leading research institution with nearly 1000 research faculty and \$428 million in grant support. State-of-the-art facilities are easily accessed by students, faculty, and staff.

VA SALT LAKE CITY HEALTH CARE SYSTEM

VA Salt Lake City Health Care System (VASLCHCS) is part of Network 19, which includes facilities in Utah, Wyoming, Montana, Colorado, Idaho, and Nevada. The George E. Wahlen Department of Veterans Affairs Medical Center in Salt Lake City is a tertiary care facility that provides a full range of patient care services. It is a state-of-the-art medical facility with an active research enterprise and educational mission. VASLCHCS has an integrated affiliation with the University of Utah on the clinical, educational, and research levels. Many VA providers have joint appointments with the University of Utah and have clinical and research efforts at both sites.

Office and Laboratory Space

Of relevance to this proposal is office and laboratory space. Dr. Raphael has an individual office in Building 2 on the VASLCHCS campus. Study coordinators, students, and other personnel share an office adjacent to Dr. Raphael's. Research offices at VA have hardwired internet connections to the University of Utah permitting direct and secure connectivity of University of Utah-issued desktop and laptop computers to the password-protected and encrypted University of Utah mainframe where data will be stored on the REDCap platform. Dr. Raphael has a University of Utah-issued laptop and a separate VA-issued laptop computer for VA business. Telephones, photocopying equipment, fax equipment, and other standard office furniture and fixtures are in place. Dr. Raphael's 700 square foot laboratory is in Building 2 on the VASLCHSC campus, directly adjacent to the offices of Dr. Raphael and his research team. The laboratory has a -80°C freezer with centralized monitoring, refrigerator with centralized monitoring, standard blood and urine processing equipment, a vacuum hood, and standard laboratory equipment (centrifuges, water bath, hot plate, magnetic stirrers, pipettes, glass-ware, pH meters. The laboratory has space for up to four individuals to work at a time.

Equipment: Dr. Raphael's laboratory has a TitroLine 5000/20 YSI Unit that will be used to measure urinary acid excretion.

Bone In CKD Alkali Response Pilot Trial (BICARb Pilot Trial) Protocol

NYU Langone Health

Dr. Melamed is a member of the Division of Nephrology in the Department of Medicine at NYU Langone Health. Her 100 square foot office is in the Translational Research Building where she has a fully equipped computer and printer. The Division of Nephrology includes 25 faculty members and has regular weekly meetings. The Division is led by Dr. David Charytan who is an R01 funded investigator in cardiovascular disease in CKD.