Title: Uric Acid Reduction as a Novel Treatment for Pediatric Chronic Kidney Disease

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RESEARCH PROPOSAL

TABLE OF CONTENTS
Page 1

ABSTRACT - Summary

Pediatric chronic kidney disease (CKD) is a devastating disease that not only limits quality of life, but life span. Although promising results have emerged from epidemiologic studies and adult CKD trials demonstrating that lowering serum uric acid (UA) levels with Xanthine Oxidase (XO) inhibitors can improve renal function and even blood pressure (BP), there is currently no well-established therapy that can reverse the rate of decline of renal function in *pediatric* CKD. A single published pediatric CKD trial using a XO inhibitor did demonstrate significant improvement in renal function and BP, however the study had some statistical and design flaws and the study findings have not yet been reproduced in the literature. Furthermore, while non-clinical studies have demonstrated that high UA leads to specific changes that promote inflammation, cardiovascular, and kidney injury, there is a lack of clinical studies showing how UA lowering therapy impacts humans. Our pilot randomized controlled clinical trial proposes to establish that the treatment of pediatric CKD patients with high UA using Allopurinol, a XO inhibitor, over a six month period can improve kidney function. We will also measure changes in biomarkers of inflammation and kidney injury after Allopurinol treatment. The results of this study will improve our understanding of UA mediated disease in pediatric CKD, and determine whether Allopurinol therapy can improve kidney function in this population.

PUBLIC HEALTH IMPACT

The incidence and prevalence of pediatric CKD and renal replacement therapy is rising throughout the world, and higher in the United States (U.S.) compared to Western Europe[1]. Various non-modifiable factors, including race and disease etiology, and modifiable clinical factors of hypertension, proteinuria, and high uric acid (UA) negatively affect the rate of renal function decline [2]. In the U.S., African American children have a two-fold higher incidence of end stage renal disease than Caucasian children but are underrepresented in many clinical trials. The Children's Hospital of Richmond at VCU Pediatric Nephrology Division has a unique CKD population composed of 50% Black race which is an important feature of this proposed clinical study. There is no therapy that has been proven to reverse renal function decline in pediatric CKD to date. However, UA lowering therapy with Xanthine Oxidase (XO) inhibitors has recently been shown to improve renal function in adults with CKD. The effectiveness of this therapy needs to be reproduced in large-scale pediatric clinical trials, and has important disease-modifying potential in the pediatric population. The XO inhibitor Allopurinol proposed for use in this pilot clinical trial is an inexpensive, universally available generic medication with a well-documented safety side effect profile in pediatrics. Although the only published pediatric CKD trial of Allopurinol had study design flaws, it showed an impressive statistically significant positive increase in renal function over 4 months of therapy compared to placebo. A pediatric CKD study which addresses these study design flaws must be reproduced before a large multi-center trial is undertaken, and is proposed in this clinical trial.

COMPLIANCE STATEMENT

I certify that this submission contains an Applicable Clinical Trial and that I will ensure compliance with registration and results reporting submissions to ClinicalTrials.gov as required under the FDA Amendments Act of 2007 and the Final Rule (42 CFR Part 11).

SPECIFIC AIMS

Chronic kidney disease (CKD) is a life-long condition with significant morbidity and premature mortality due to progressive decline in renal function towards end stage renal disease (ESRD). Once on dialysis, the expected remaining lifetime for a child with pediatric-onset ESRD is 18 years [3]. With mortality rates 30-150 times higher than the general pediatric population, the management of CKD to prevent or slow the progression of renal dysfunction is crucial. Pediatric-onset CKD originates predominately from congenital anomalies of the kidney and urinary tract (CAKUT, 50%), glomerular disorders (22%), and other hereditary nephropathies whereas the majority of adult-onset CKD is due to chronic diabetes and hypertension (HTN). Differences in disease etiology (glomerular vs. non-glomerular), race, and having modifiable conditions of proteinuria, hyperuricemia, or HTN significantly impacts CKD disease duration and rate of progression [4, 5]. Both the strict control of blood pressure (BP) and reduction of proteinuria are incompletely effective and can only slow the rate of renal function decline [6].

The association of faster CKD progression with hyperuricemia is a relatively recent discovery resulting from large epidemiologic studies [7, 8]. Historically hyperuricemia was defined by a serum uric acid (UA) level >6.8-7 mg/dL, the supersaturation point of UA in the blood at physiologic pH. However, there is a growing body of literature that identifies an increased risk for acute kidney injury, incident CKD, and HTN at UA levels lower than this historical definition [9-11]. Animal models and *in vitro* studies confirm that mild hyperuricemia below the supersaturation point induces: 1) a reversible endothelial dysfunction through the production of oxygen radical species [12], 2) HTN through activation of the renin-angiotensin system [13], 3) activation of pro-inflammatory mediators through the Nlrp3 inflammasome [14], and 4) both direct UA-mediated and indirect Nlrp3-mediated renal dysfunction through tubular injury and modification of the renal vasculature [15, 16]. As a result, hyperuricemia is increasingly defined as a serum UA level ≥5.5-6 mg/dL in clinical trials [17, 18].

Adult CKD clinical trials of Xanthine Oxidase (XO) inhibitors, which block the production of UA via the enzyme XO, have reduced UA and increased renal function, i.e. the glomerular filtration rate (GFR), over trial periods of 12 weeks to 2 years [19-21]. To date, only one 4-month pediatric CKD trial has been published by Sharbaf et al that showed treatment with Allopurinol, a XO inhibitor, improved GFR by a mean increase of +16 ml/min/1.73m^2, SD=9.3 compared to placebo [18]. The treatment also demonstrated a significant improvement in BP similar to another clinical trial of Allopurinol in a randomized 4-week crossover trial of hyperuricemia in pediatric essential hypertension [17]. The Sharbaf trial (2018) had study design flaws in that it did not use intention-to-treat principles, was not stratified for known modifiers of GFR decline, and did not report race. Additionally, none of the aforementioned clinical trials have explored the mechanism of how XO inhibitors improve GFR or BP, revealing an area for research. If benefits of GFR improvement from XO inhibition are reproduced in a well-designed pediatric CKD trial, this therapy could potentially offer hyperuricemic patients a significant improvement in disease burden. **We propose here a pilot clinical trial to identify the rate of GFR change following 6 months of Allopurinol treatment versus standard of care amongst pediatric hyperuricemic CKD patients. We hypothesize that Allopurinol therapy will reduce serum UA level and improve the rate of GFR change.** We will simultaneously explore a possible mechanism of Allopurinol therapy via reduced Nlrp3 inflammasome activity and expect to see a reduction of renal injury biomarkers. This study will address the feasibility of a design that stratifies the population for known modifiers of GFR decline with adequate power, essential preliminary data for designing a future large-scale multicenter pediatric trial.

Aim 1. To determine the effect of Allopurinol treatment on GFR of hyperuricemic pediatric CKD patients. In a randomized controlled study, pediatric CKD patients with hyperuricemia (serum UA ≥5.5 mg/dL) will be allocated 2:1 to Allopurinol versus standard of care (SOC) control for 6 months. Participants will be stratified into two cohorts by disease etiology (cohort A: non-glomerular, cohort B: glomerular). Equal allocation of race is expected as our local population is composed of 50% black race. The primary outcome measure is the amount of GFR change from baseline to 6 months compared to the control group in both cohorts. Secondary outcomes are measurement of the amount of UA and BP change from baseline to 6 months.

Aim 2. Establish whether Allopurinol treatment reduces Nlrp3 inflammasome and renal injury biomarkers. In this exploratory aim, urine and serum biomarkers of Nlrp3 inflammasome activation (hs-CRP, XO enzyme activity, Nlrp3, IL-1β, IL-18) and renal injury (KIM-1, ET-1, NAG, and NGAL) will be collected at 3 and 6 months and compared to baseline of cohorts A and B treatment and control groups.

Impact: GFR change from baseline to 6 months by treatment and cohort will be used to directly inform the effect size and sample size calculations required for a randomized controlled multicenter pediatric intervention trial. The simultaneous and novel exploration of the effect of XO inhibition on inflammation and renal injury biomarkers will provide crucial data that may identify mechanism of the XO inhibition effect.

BACKGROUND AND SIGNIFICANCE

Uric acid (UA) is a purine nucleotide and fructose breakdown product via the enzyme Xanthine Oxidase (XO) which also generates harmful reactive oxygen species (ROS) byproducts. Two-thirds of serum UA is excreted by the kidneys through multiple regulation transporters, which can become inefficient in chronic kidney disease (CKD). Hyperuricemia develops by increased UA production, for example through a high purine meat or fructose diet, impaired renal UA excretion, or both. Large epidemiologic studies have recently associated hyperuricemia with incident acute and chronic kidney injury, a faster rate of renal function decline in both pediatric and adult chronic kidney disease (CKD), and an increased risk for death in CKD and dialysis patients [4, 8]. UA-mediated damage occurs along a “J” shaped pattern of injury, where it functions as a powerful anti-oxidant at mid-range levels and pro-oxidant at the extremes [10, 22]. Rat models of hyperuricemia show that mildly elevated UA causes crystal-independent renal injury through direct activation of the renin-angiotensin system, endothelial dysfunction through NADPH oxidase activation and ROS release [12]. In these animal models, induction of a mild hyperuricemia also results in pathologic changes to the renal functional nephron unit, i.e. glomerular hypertrophy and hyperfiltration, afferent arteriolar constriction, and tubular fibrosis which can be reversed with Allopurinol, a XO inhibitor [16].

Adolescents with UA levels above 5.5 mg/dL in the National Health and Nutrition Examination Survey (NHANES) 1999-2006 had a 2-fold increased odds of elevated blood pressure (BP)[9]. This value has since been used as a pediatric definition for hyperuricemia in several clinical studies and applied in this proposal [15, 17, 18]. A cross-over randomized controlled trial also demonstrated reduction of UA significantly improved systolic and diastolic BP in pediatric essential hypertension patients with hyperuricemia[17]. Clinical trials of XO inhibitors in adult CKD patients have demonstrated a reduced rate and in some, a reversal of decline in glomerular filtration rate (GFR) [21].

Pediatric CKD epidemiology is different from adult CKD in the following ways. First, the etiology is primarily due to non-glomerular diseases (e.g. congenital anomalies of the kidney and urinary tract [CAKUT], the most common cause at 50%), and glomerular diseases (e.g. acute glomerulonephritis) rather than the primary adult causes of diabetes and hypertension. CAKUT conditions and the resultant, often insidiously progressive, CKD is present from birth. Whereas the typical age of onset of glomerulonephritis is the teenage years with acute onset renal dysfunction leading often to a more rapid chronic progressive disease than non-glomerular CKD. In pediatrics, factors that affect the rate of renal function decline and lead to a faster progression of CKD towards end stage renal disease (ESRD) are black race, glomerular disease etiology, and modifiable disease phenotypes of hypertension, proteinuria, and hyperuricemia [2, 4].

Results from adult clinical trials are often extrapolated to the pediatric population, but with the above listed differences in CKD epidemiology, the beneficial effect of UA lowering therapy should be tested separately in pediatrics. The effect of UA lowering therapy may differ for those with glomerular versus non-glomerular disease etiology, race, or for those with proteinuria versus none. There are data to support a similar beneficial effect from XO inhibitors in pediatrics as in adults, but the effect modification, if any, of these factors is not specifically known. For example, a single randomized placebo-controlled pediatric CKD trial of Allopurinol for 4 months demonstrated a statistically significant increase in the mean glomerular filtration rate (GFR) from baseline to endpoint of +16 ml/min/1.73m2 (SD=9.3). However, this study did not report race, did not stratify participants by glomerular or non-glomerular disease etiology or presence of proteinuria, and did not use intention to treat principles when those with a pre-specified adherence rate <80% were excluded at the end of the study, leading to an overall study power of 78%. The reported rate of GFR change in adult trials range from approximately +1 to +3 ml/min/1.73m^2 (SD=1-3) [20]. While we recognize results in pediatric populations may differ from adults, further confirmation is needed before progressing to large scale trials. A feasibility pilot clinical trial proposed here will test the effect of XO inhibition on GFR using study design principles of blocked allocation of participants to control for known factors that affect GFR decline.

RESEARCH METHODS – Study Design

Specific Aim 1. To determine the effect of Allopurinol treatment on GFR of pediatric CKD patients with hyperuricemia.

1.1. Rationale and Objective: While there is support in the literature for beneficial effect of XO inhibitor therapy on GFR and BP in pediatric CKD, the degree of expected change in GFR based on disease etiology is uncertain. Therefore, we propose a randomized controlled trial of hyperuricemic pediatric CKD participants in a 2:1 allocation between Allopurinol and standard of care (SOC) therapy, and stratified by disease etiology (cohort A: non-glomerular, cohort B: glomerular). Randomization procedure will be blinded, but the allocation will be unblinded to investigator and participant because of the lack of placebo. Allopurinol will be titrated to reach a normal range of serum UA 3-5 mg/dL by 6 months. Local SOC practice for pediatric CKD includes control of blood pressure with anti-hypertensives, control of acidosis, control of proteinuria, and frequent laboratory monitoring to measure the rate of renal function decline. The primary outcome of Aim 1A is change in GFR between baseline and 6 months by treatment group. The secondary outcomes are change in serum UA, and change in BP over the same time. An exploratory sub-aim (Aim 1B) will identify and compare GFR change by cohort characteristics (disease etiology, proteinuria, and race) that may influence future trial designs.

1.2. Experimental Design (**Table 1**): We will conduct a 6-month randomized treatment (Allopurinol) vs. SOC clinical trial to measure change in GFR over time in pediatric hyperuricemic CKD participants. We will conduct this study after obtaining appropriate consent and assent. Our recruitment pool will include all patients receiving medical care from the CHoR Pediatric Nephrology Division, new and recurring outpatient encounters. The division currently sees approximately 3,500 outpatient encounters per year. The study visits will coincide with SOC visits with the possible exception of visit V1A (some but not all participants will normally be seen for SOC 1 month after the baseline visit). The following inclusion and exclusion criteria apply:

- Inclusion Criteria: CKD stage 1-5; Age 2-20 years old at time of enrollment; Hyperuricemic
- Exclusion Criteria: Contraindication to Allopurinol; Elevated baseline liver function tests; Receiving acute or chronic dialysis; Primary metabolic disorder; Sickle cell disease; Autosomal Dominant Polycystic Kidney Disease; Cystinosis; Bartter or Gitelman Disease; Pregnant or nursing.

The allocation will be unblinded to investigators and participants. We plan to over-sample the glomerular cohort B and limit enrollment of the non-glomerular cohort A to ensure adequate distribution of the sample by disease etiology in a proportion generalizable to the national pediatric CKD population (2:1). The proposed allocation distribution is detailed in Section 1.3 and **Table 2**.

Hyperuricemia is defined in this protocol as having at least two measures of serum UA ≥5.5 mg/dL in the last 12 months, or actively treated with a XO inhibitor for a previous diagnosis of hyperuricemia. Participants actively treated with a UA lowering agent (Allopurinol, Febuxostat, or Losartan) will undergo a washout period of a minimum of 1 month (up to 3 months) prior to enrollment in the trial, then randomized to treatment versus control groups. None of the patients in the CHoR Pediatric Nephrology group practice actively treated with these agents had/have symptomatic hyperuricemia, and only 3 out of 14 treated have reached the target UA level of 3-5 mg/dL which will be applied in this study protocol. As it is unknown to what degree patients are benefiting from a minimal reduction of UA but with a persistent hyperuricemia, the CHoR Pediatric Nephrology Division has concluded that it is ethical for consenting participants actively receiving a XO inhibitor to be randomly assigned to treatment or control after a wash-out period.

Allopurinol dose will be initiated using standard weight-based dosing at the Baseline Visit 1 (V1), and titrated at Visits 1A and 2 (V1A, V2) to achieve a goal UA level in the normal range of 3-5 mg/dL by Visit 3 (V3).

At baseline, demographic and anthropometric data, CKD disease etiology and duration since diagnosis, current medications, and presence of proteinuria or hypertension will be collected. At baseline and 6 months, casual clinic BP will be obtained (the average of three measurements) for hypertension assessment. Serum and non-invasively obtained urine will be collected at baseline, 3, and 6 months for basic or comprehensive metabolic panel, UA, cystatin C and creatinine-based GFR measurements. An additional serum and urine sample for purposes of dose titration and safety will be collected from the treatment group but not control at Visit V1A. The residual serum and urine samples will be bio-banked for the analyses of Aim 2. Adverse events will be collected and adherence will be measured at the V1A, V2, and V3 visits by pill count and through a validated visual analogue scale of adherence [26]. Participants will also receive a one-time monetary compensation at the conclusion of the study (V3).

Table 1. Study Timeline and Data Collection

Study Visit	Subject identification	Baseline Visit (V1)	Visit 1A (V1A)	Visit 2 (V2)	Endpoint Visit (V3)
Time	-1 to -3 months	0	+1 month	+3 months	+6 months
Encounter Purpose	1-3 month Allopurinol washout	Study enrollment, Randomization, baseline values	UA titration, Adherence & Safety check	UA titration, Adherence & Safety check	Study endpoint
Data Collection of Treatment group	C, G	A-E, G	D, F	C, E, F	A-F
Data Collection of Control group	C	A-E	No visit	C	A-E
Data Collection key	A: Demographic, anthropometric, medication history, clinic BP B: Vital signs including 3 casual clinic BP measurements C: Standard of care lab work: Serum – Basic metabolic panel, UA, cystatin C; Urine – Protein, creatinine, UA D: Serum Comprehensive metabolic panel; urine UA, creatinine. E: Reserve residual serum and urine samples for biomarker analysis F: Pill count, Adherence visual analogue scale, Evaluation of adverse events G: Urine pregnancy test if applicable to females of reproductive age				

1.3. Statistical Analysis: We will report means/medians and standard deviations (SD)/interquartile range (IQR) for all continuous measures, and frequency and proportions for categorical variables. Assuming a clinically significant difference between treatment groups of 3 ml/min/1.73m^2 and individual group SDs=3.5, a one-sided analysis t-test performed at α=0.05 will achieve at least 80% power for a sample size of 42 if the participants will be allocated in a 2:1 ratio between treatment and control. We will also enroll participants into two cohorts to assure proportional distribution between non-glomerular (cohort A) and glomerular (cohort B) disease etiology. Our local pediatric CKD population composition by disease etiology is similar to national proportions of approximately 70% non-glomerular and 30% glomerular disease etiology. We will therefore over-sample the glomerular sub-population in cohort B and limit enrollment of the non-glomerular cohort A to n=19, maintaining roughly a 2:1 proportion. The goal allocation enrollment by treatment group and cohort size is summarized in **Table 2**. Two-sample t-tests on the GFR change score will be used to address Specific Aim 1A while separate 2-way ANOVA models with an interaction will be used to address Aim 1B. Repeated measures ANOVA models will be used to inform from all three time points in an intent-to-treat fashion.

Table 2: Goal allocation enrollment

Treatment Group	Allopurinol Group	Control Standard of Care Group
Cohort A: Non-glomerular disease etiology	19	7
Cohort B: Glomerular disease etiology	9	7
Total	28	14

Specific Aim 2. Determine the effect of Allopurinol treatment on Nlrp3 inflammasome and renal injury biomarkers.

2.1. Rationale and Objective: To our knowledge there are no studies that explore the effect of XO inhibition on the known mechanism of hyperuricemia induced Nlrp3 inflammasome activation and renal injury in a clinical trial setting. We therefore propose to establish whether XO inhibition reduces levels of these biomarkers at 3 and 6 months compared to baseline. If our hypothesis is correct that inflammasome-mediated renal injury is improved by Allopurinol, we expect to find that after 3 and 6 months of Allopurinol treatment, the biomarker levels will be reduced from baseline in both treated cohort groups compared to control participants.

2.2. Experimental Design: The study design of Aim 2 is the same as Aim 1 (see **Table 2**). We will measure the following biomarkers from reserved serum and urine samples at the baseline, 3, and 6 month visits. Activity of the Nlrp3 inflammasome will be measured via: serum high sensitivity CRP, Xanthine Oxidase

activity level, Nlrp3, Interleukins 1β and 18, and urine Nlrp3 and IL-18. Renal injury biomarkers will be measured from serum NGAL, urine NGAL, NAG, KIM-1, and ET-1.

2.3. Statistical Analysis: We will report means/medians and standard deviations (SD)/interquartile range (IQR) for all continuous measures. Similar analyses will be used for Specific Aim 2 as Specific Aim 1. All sample size calculations were performed with nQuery Advisor v.7.0.

STUDY INTERVENTION ADMINISTRATION

The proposed intervention uses a study drug (Allopurinol) and concomitant therapy (Candesartan) that are available as generic. The PI is proposing to study the effects of Allopurinol under FDA-approved indications, which is approved for use in children and adults for the reduction of high uric acid levels. Candesartan is approved for use in children and adults for the reduction of high blood pressure. The concomitant therapy, Candesartan, is required in this protocol to reduce drug-drug interactions with Allopurinol. The medications Lisinopril, Enalapril, and Benazepril are commonly prescribed for hypertension but increase the risk of moderate to severe adverse reactions when used concomitantly with Allopurinol. Losartan is also a blood pressure lowering medication that uniquely lowers uric acid levels which could affect the results of the trial, but does not interact with Allpurinol so will be converted for a different and specific reason. Any participant in the trial who is prescribed Lisinopril, Enalapril, Benazepril, or Losartan at the time of randomization will be converted to a similar or same class of blood pressure lowering medication, Candesartan, which does not interact with Allopurinol or lower uric acid levels. Approximately 1/4 of participants in this trial will qualify for the Candesartan conversion. Candesartan will be supplied by the investigational pharmacy at no cost to participants. Allopurinol will also be supplied by the investigational pharmacy to the treatment group participants.

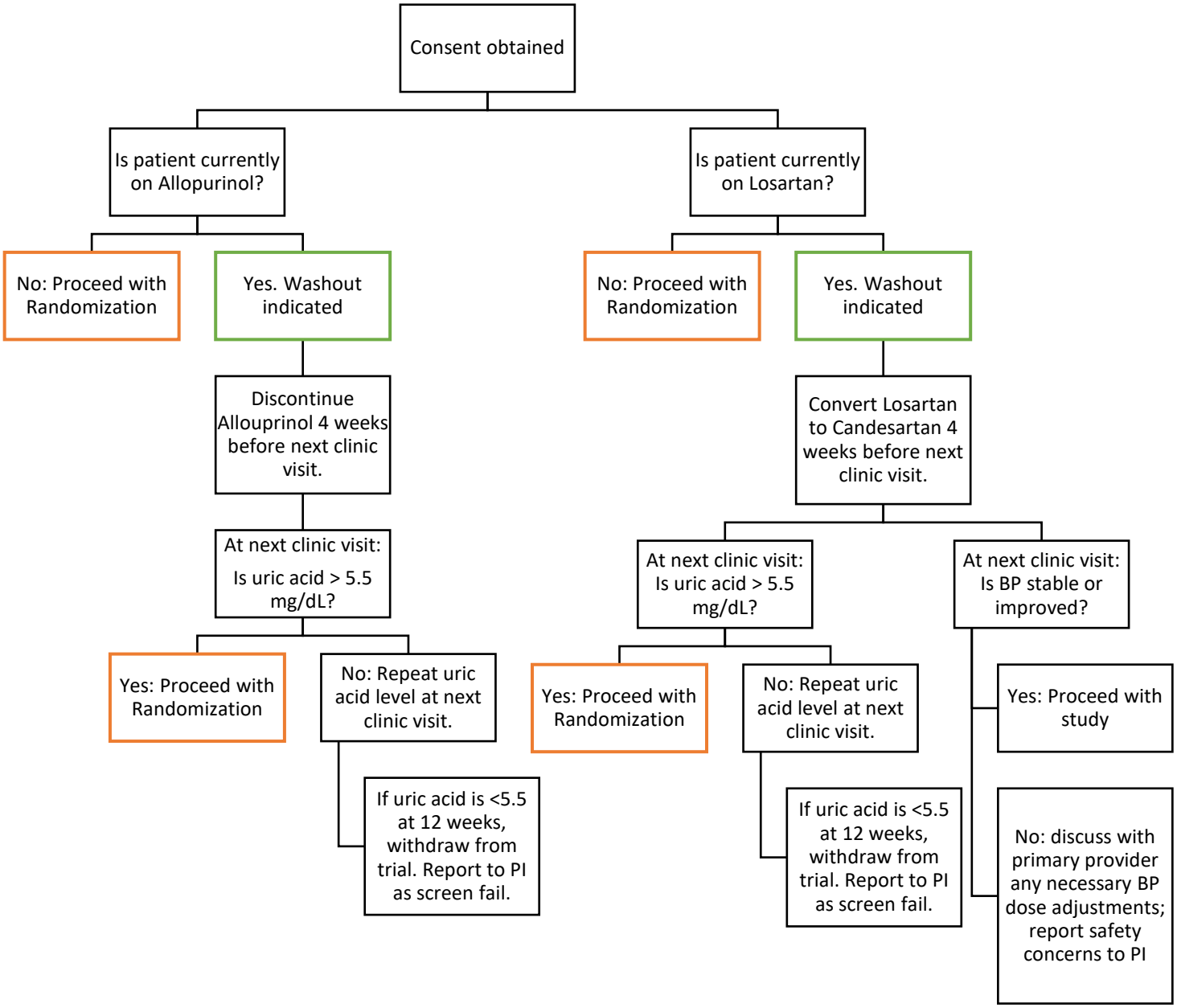
Recruitment and pre-trial medication adjustments:

Participants will be recruited during a standard of care (SOC) visit and consented at that visit or by phone if they meet study criteria. Subjects will be randomized in a blinded manner to treatment or control groups at the time of consent if they do not require a washout or medication conversion. If they do require a washout or medication conversion to Candesartan, the randomization will occur once the washout is completed and after a If applicable, the Allopurinol washout and/or Candesartan conversion will be initiated 4 weeks before the participant's next scheduled SOC visit. In the case of Allopurinol washout, the PI or research coordinator will provide the participant with the Allopurinol stop-date and call the participant to remind them to discontinue within 7 days of the medication change. Uric acid level will be measured with SOC labs at their next SOC visit and if participants are hyperuricemic (UA≥5.5 mg/dL), will continue in the trial in their pre-determined treatment group. However if participants are normouricemic (UA <5.5 mg/dL), UA will be checked again at their next SOC visit up to 3 months later, and participants will proceed in the trial if they are then hyperuricemic. Otherwise they will be withdrawn from the trial, and their primary nephrology provider will decide whether to resume or discontinue Allopurinol treatment off-study at their own discretion.

In the case of Candesartan conversion, the PI along with consultation from the participant's primary nephrologist will prescribe the starting dose of Candesartan. The PI or research coordinator will instruct the participant to STOP Losartan/Lisinopril/Benazepril/Enalapril and START Candesartan on a specific date scheduled 4 weeks before their next SOC visit. The research coordinator or PI will confirm the start/stop date with the participant by phone within 7 days, and if unable to reach the participant or his/her guardian, the Candesartan will NOT be mailed to the participant by the investigational pharmacy. The participant's BP will be checked at their next SOC visit as part of routine care, and their primary nephrologist will make adjustments to the medication as necessary to achieve adequate BP control. If a participant decreases or remains in the same stage of hypertension (as defined by national pediatric BP guidelines) as before the Candesartan conversion (for example, remains in Stage 1 hypertension pre- and post-Candesartan, or moves from Stage 1 to normal pre- and post-), then the participant may continue in the trial. If, however, the participant increases in hypertension stage pre- and post-Candesartan conversion (for example, normal to Stage 1 hypertension pre- and post-) the primary nephrologist will either adjust the Candesartan dose or decide to withdraw the participant from the trial and revert back to the prior medication as they deem necessary. Similarly, if the BP is determined to be too low, the dose will be adjusted or discontinued by the primary nephrologist. Signs and symptoms of low BP will be reviewed with participants prior to the conversion, and participants will be

encouraged to report any symptoms once they are converted. Participants who experience side effects, or those that are withdrawn from the study due to Candesartan conversion will be reported to the PI/research coordinator and Independent Monitor. The Data and Safety Monitoring Plan documents will review this in more detail.

Figure 1. Washout and Medication Conversion Decision Tree



The investigational pharmacy (IP) will purchase the generic Allopurinol and Candesartan tablets, the cost of which is included in the IP's administrative fees. This is a pilot clinical trial that uses a standard of care control group. It does not involve placebo encapsulation or blinding. The IP is responsible for packaging, labeling, and distributing the study drug Allopurinol as well as the concomitant therapy, Candesartan.

DOSING OF ALLOPURINOL: We will utilize a weight-based dosing strategy, starting at 5mg/kg/day divided twice daily. A maximum daily dose per day will be restricted at 400 mg per day. **Table 3** lists the starting dose by weight range.

Table 3. Allopurinol weight-based starting dose

Weight range	Dose
15-25 kg	50 mg TWICE DAILY
25.1 – 35 kg	75 mg TWICE DAILY
35.1 – 50 kg	100 mg TWICE DAILY
50.1 – 70 kg	150 mg TWICE DAILY

To target a uric acid level of 3-5 mg/dL used in this protocol, the Allopurinol dose will be escalated at Visit 1A and Visit 2 if the participant's uric acid level is >5 mg/dL. Similar to other Allopurinol dose escalation trials, the dose will be increased by 50mg/d for those participants with an estimated glomerular filtration rate (GFR) <60ml/min and 100mg/d in those with GFR ≥60ml/min.

DOSING OF CANDESARTAN: We will utilize an age and weight-based dosing strategy as recommended by the FDA dosing guidelines (**Table 4**). The participant's doctor is responsible for titrating Candesartan within the recommended dosing range to achieve the desired blood pressure control.

Table 4. Candesartan age and weight-based starting dose and dosing range

Age	Starting Dose	Titratable Dose Range
1 to <6 years	0.2 mg/kg once daily	0.05 – 0.4 mg/kg daily
6 to <17 years		
<50 kg	4-8 mg once daily	4-16 mg once daily
>50 kg	8-16 mg once daily	4-32 mg once daily
>17 years	16 mg once daily	8-32 mg total daily dose

DATA AND SAFETY MONITORING PLAN

This randomized controlled trial aims to test the hypotheses that treatment of hyperuricemia with a xanthine oxidase inhibitor (Allopurinol) reduces the rate of decline of kidney function in chronic kidney disease, and markers of renal injury and inflammation. The Data and Safety Monitoring Plan (DSMP) is outlined below. During this study, all data collected will be kept confidential in an encrypted database using identification codes. Only approved research team members will have access to the database. The study staff will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance. Reviews of subject accrual, including compliance with protocol enrollment criteria and adherence data, will be performed by the PI and study staff on a monthly basis.

Data on adherence to the treatment protocol will be collected on an ongoing basis by research staff and reviewed quarterly by the PI. Adherence of participants will be evaluated by performing pill counts at study visits and by a validated visual analogue scale of adherence (patient self-report) at the end of study visit. An intention to treat protocol is applied to this study. However, if adherence falls below a rate of 75% which might inhibit the ability of the study to test its primary hypotheses, the study investigators and statistician will convene to discuss methods for improving adherence.

The PI will designate an Independent Monitor to perform an independent review of ongoing study progress and safety. The Independent Monitor will not be a part of the key research personnel, and will be qualified to review the patient safety data. Progress reports, including patient recruitment, retention/attrition of the study as a whole as well as retention of subjects undergoing washout or conversion therapy to study initiation, and adverse events (AE), will be provided to the Independent Monitor every 6 months. The reports will be generated only from aggregate for the entire study population. A closed safety report with masked group assignment will be generated for the Independent Monitor by an unmasked member of the study team (research coordinator).

An Annual Report will also be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions

whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Monitor and will be forwarded to the IRB.

AE reports and annual summaries will not include identifiable material. Each report will refer only to the subjects' identification code. An AE is any untoward medical occurrence in a subject during participation in the clinical study or with use of the intervention agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, skin reaction or physical exam finding), or any combination of these. A serious adverse event (SAE) is any adverse event that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- An important medical event based upon appropriate medical judgment

AEs will be labeled according to severity, which is based on their impact on the patient. An AE will be termed "mild" if it does not have a major impact on the patient, "moderate" if it causes the patient some minor inconvenience, and "severe" if it causes a substantial disruption to the patient's well-being. AEs will also be categorized according to the likelihood that they are related to the study intervention and labeled: definitely unrelated, definitely related, probably related, or possibly related to the study intervention. AEs will be reviewed with participants at each study visit.

Occasional 1-10% mild AEs are mild nausea, mild elevation in liver transaminase levels, and are not expected to impact a patient. These risks are considered minimal and will be addressed in the protocol and consent form.

The rate of moderate AEs is expected to be <1%. The protocol includes measures to reduce the risk of moderate to severe AEs. Moderate AEs include skin reaction, gastrointestinal distress, moderate elevation in liver transaminases. Subjects will be encouraged to report these occurrences at any time during the intervention period by telephone within 24 hours of experiencing an event. Any adverse event rate over 5% in 12 months will be reported to the IRB.

Severe AEs include skin reaction as with development of Stevens-Johnson syndrome, or a significant elevation in liver transaminase levels that require hospitalization, and will be reported immediately to the IRB if this occurs. SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Monitor and IRB in accordance with requirements. The Independent Monitor will be a clinician appointed by the PI who is not involved with the study design or analysis and is not a study investigator.

Unexpected fatal or life-threatening AEs related to the intervention will be reported to the IRB within 7 days. Other serious and unexpected AEs related to the intervention will be reported to the IRB within 15 days. Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Monitor and IRB. In the annual AE summary, the Independent Monitor Report will state that they have reviewed all AE reports.

The study staff, PI, and Independent Monitor will review the conglomerate adverse event rates every 6 months. Review of AE and SAE reports will also occur on an ongoing basis by the PI and study staff.

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.