PREVENTION OF URINARY STONES WITH HYDRATION (PUSH)

A randomized clinical trial to investigate the impact of increased fluid intake and increased urine output on the recurrence rate of urinary stone disease (USD) in adults and children

STUDY PROTOCOL

Protocol Identifying Number: USDRN01

Principal Investigator(s): Charles D. Scales, Jr., MD MSHS

Hussein R. Al-Khalidi, PhD

Funded by: **National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)**

Version Number: 5.0

Date: February 4, 2020

NCT03244189

Table of Contents

LIST OF ABBREVIATIONS

AUA	American Urological Association
CASUS	Comprehensive Assessment of Self-reported Urinary Symptoms
CC	Clinical Center
DSMB	Data and Safety Mointoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMR	Electronic Medical Record
FI	Financial Incentive
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IRB	Institutional Review Board
LAR	Legally Authorized Representative
LUTS	Lower Urinary Tract Symptoms
MOP	Manual of Procedures
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
PI	Principal Investigator
PUSH	Preventing Urinary Stones with Hydration
RBM	Risk-Based Monitoring
SPS	Structured Problem Solving
SDRC	Scientific Data Research Center
UOP	Urine Output
USD	Urinary Stone Disease
USDRN	Urinary Stone Disease Research Network
WTH	Way to Health

STATEMENT OF COMPLIANCE

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will personally oversee the conduct of this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision with copies of the protocol. I will discuss this material with them to ensure that they are fully informed about the efficacy and safety parameters and the conduct of the study in general. I am aware that, before beginning this study, the Institutional Review Board responsible for such matters must approve this protocol in the clinical facility where it will be conducted. I agree to make all reasonable efforts to adhere to the attached protocol.

I agree to provide all study participants with informed consent forms, as required by government and International Conference on Harmonization regulations. I further agree to report to the sponsor any adverse experiences in accordance with the terms of this protocol.

_____
Principal investigator Name (print)

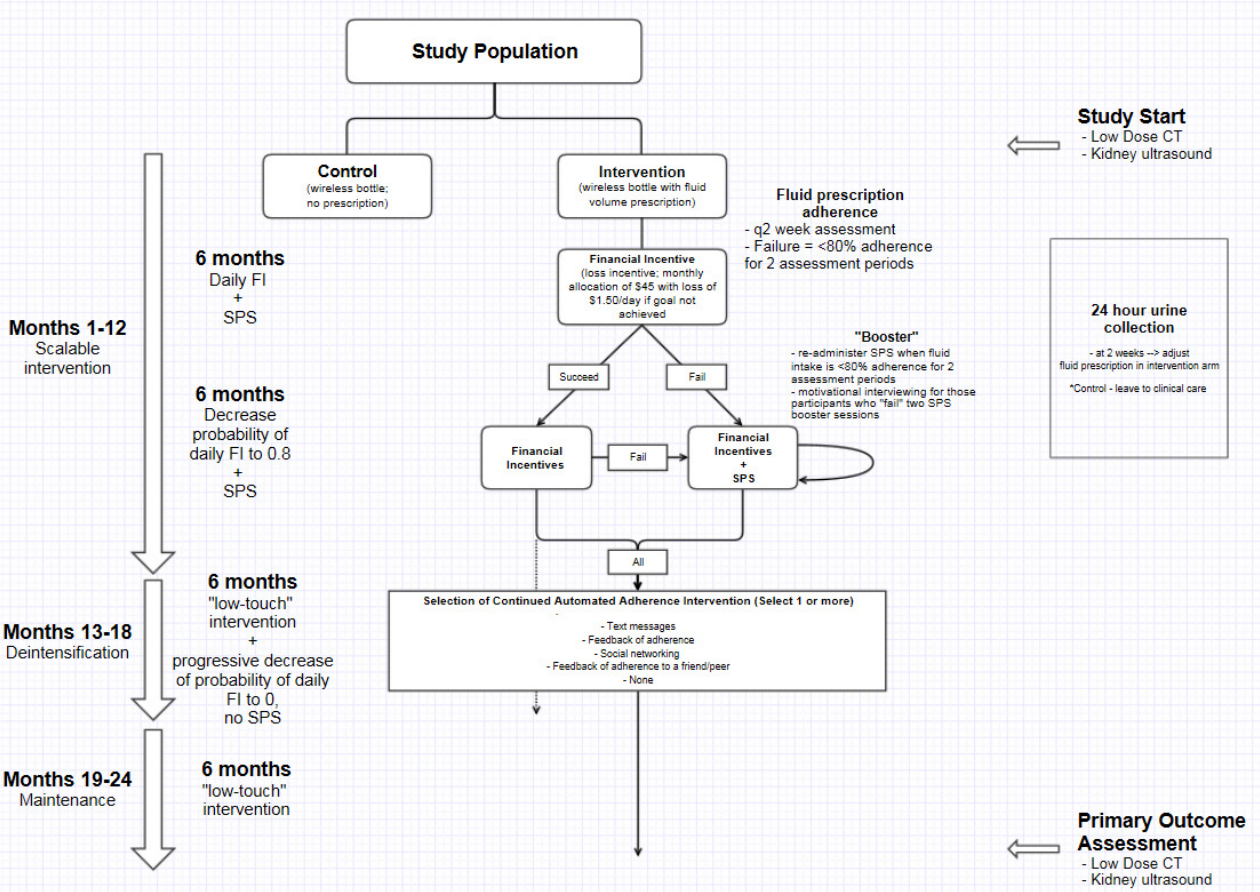
_____
Signature

_____
Date

PROTOCOL SUMMARY

Protocol Number	USDRN01
Protocol Title:	Prevention of Urinary Stones with Hydration (PUSH)
Main Criteria for Inclusion:	Study participants ≥ 12 years of age with ≥ 1 symptomatic stone event in past 3-5 years
Study Objectives:	To determine whether a multi-component program of behavioral interventions will result in reduced risk of stone disease recurrence/progression over a 2 year period.
Study Design:	Randomized, blinded, prospective clinical trial
Intervention Regimen	Behavioral intervention program
Duration of Study Participation	24 months
Duration of Study Overall	4 years
End-of-study Definition	Last study participant completion of 24-month follow-up
Number of Study Participants	Approximately 1642
Number of Clinical Centers:	6
Primary Endpoint:	Symptomatic stone event
Secondary Endpoints:	Asymptomatic stone recurrence Stone growth Fluid intake adherence Urine volume Cost identification

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

Charles D Scales, Jr (SDRC PI, Duke Clinical Research Institute)

Hussein Al-Khalidi (SDRC Stats PI, Duke Clinical Research Institute)

Greg Tasian (CC PI, Children's Hospital of Philadelphia/University of Pennsylvania)

Peter Reese (CC co-PI, University of Pennsylvania)

Naim Maalouf (CC PI, University of Texas Southwestern Medical Center)

Jonathan Harper (CC PI, University of Washington)

Hunter Wessells (CC co-PI, University of Washington)

Henry Lai (CC PI, Washington University, St Louis)

Alana Desai (CC co-PI, Washington University, St Louis)

John Lieske (PI, Mayo Clinic, Rochester)

Sri Sivalingam (PI, Cleveland Clinic)

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Urinary stone disease (USD) in the United States is an important medical, scientific, and public health problem. The prevalence of urinary stones has nearly doubled in the past 15 years[1] and health care utilization for treating patients with stones has risen in parallel.[2,3] USD affects 1 in 11 persons in the United States, a prevalence similar to that of diabetes.[1] Estimates from the Urologic Diseases in America project suggest that aggregate expenditures for treating study participants with urinary stones exceeds $10 billion, making USD one of the most expensive urologic conditions.[2]

Fluid intake is an appealing intervention for the secondary prevention of USD because it is effective, low risk, and inexpensive.[4-7] In a randomized trial of adults with urinary stones, fluid intake that resulted in a urine output greater than 2L/day decreased stone recurrence by 55% and increased the time to recurrence by more than 1 year.[4] Although stone formers are routinely counseled to drink more fluids, the average increase in 24-hour urine volume among adults with USD is only 300mL,[8] suggesting that adherence to fluid intake recommendations is low even when the risks of non-compliance are severe. Identifying ways to change behaviors to decrease USD recurrence is an area in need of research.[9]

2.2 RATIONALE

Most therapies for USD are directed toward treating an acute stone episode. Review of current prevention-focused guidelines reveals substantial divergence on recommendations by different organizations and a surprising number of recommendations based on expert opinion.10,11 Current guidelines do agree, however, on one fundamental lifestyle change for USD prevention: maintaining a high oral fluid intake resulting in high urine output (UOP). Therefore, an interventional trial targeting adherence to high oral fluid intake offers potential for supporting novel secondary prevention strategies for USD patients.

Substantial evidence exists for the efficacy of adherence interventions grounded in Contingency Management Theory and behavioral economics. For example, appropriately structured financial incentives (FI) can lead to improvements in smoking cessation,[12-15] weight loss,[16-19] substance abuse management[20-22] and medication adherence.[23-25] The Contingency Management perspective on behavior change is built upon B.F. Skinner's[26] studies of operant conditioning, which showed how many behaviors are acquired and reinforced by environmental contingencies. Contingency Management therefore attempts to modify behavior by changing the consequences of the behavior.[27] In a complementary way, behavioral economics research has examined how common decision errors contribute to health risk behaviors, such as lack of fluid intake, and suggests ways in which these decision-errors can also be used to structure successful interventions to improve health. We will apply FI to help maintain high fluid intake among USD study participants.

Other behavior change research has examined Structured Problem Solving (SPS) as a means to improve medication adherence and self-management.[28-30] SPS addresses behavior change by: a) identifying personal barriers to change, b) identifying feasible solutions the patient is able to implement, and c) continually evaluating the efficacy of the approach. Some studies have examined the role of self-monitoring, social interventions (e.g., peer feedback, team competition) and device-based reminders to improve adherence behaviors. While many of these interventions have been evaluated in isolation and over relatively short durations (<1 year), a key unanswered question is whether these interventions can be integrated to foster durable behavior change.

Increasingly, researchers are conducting pragmatic, multi-component trials to improve outcomes and care delivery.[31-33] Therefore the proposed study will test a theory-based program of interventions directed towards maintaining a high fluid intake. A key secondary goal of the proposed trial will be to add to the evidence base regarding fluid for prevention of urinary stones. Existing guideline recommendations for increased fluid intake to prevent stones derive from two randomized clinical trials (RCT) of increased fluid intake.[4,34] One RCT demonstrated a reduced risk of stone formation (RR 0.45, 95% CI 0.24 – 0.84) over a five year period,4 although the trial has been rated as poor quality due to unclear allocation concealment, lack of blinding and use of analytic methods that did not adhere to intention-to-treat principles.[35] The other randomized trial provided insufficient evidence regarding the intervention due to a low number of outcome events.[35] Both trials included only adult study participants, and therefore the generalizability of fluid intake for secondary stone prevention among children remains unclear. Thus, an important gap in evidence exists for a key component of guideline-based secondary prevention.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

The research involves the collection of protected health data. There is a small risk of loss of confidentiality but the researchers have in place several mechanisms for reducing this risk as described below (see section 13.4). There is also a potential risk of water intoxication leading to hyponatremia. The likelihood for this event is low, but theoretically possible. The investigators will mitigate this risk by excluding study participants with a prior history of hyponatremia or diseases and conditions predisposing an individual to hyponatremia. Furthermore, study participants will be counseled regarding the risk of hyponatremia from consumption of water beyond the recommended volume, as well as symptoms and consequences of severe hyponatremia.

2.3.2 KNOWN POTENTIAL BENEFITS

All participants in PUSH will receive educational information on the importance of fluid intake. Through participation in this study, each participant will have the potential to increase their fluid intake, which could improve their health and reduce their risk for future USD. If this approach is effective, it could have tremendous benefits for society if adopted on a wide scale to help individuals increase fluid intake

after experiencing a urinary stone event. It is expected that other people will gain knowledge from this study and that participation could help clinicians and study participants understand how to effectively motivate increased fluid intake and reduce the risk of kidney stones.

Children and families, as well as adult participants, will have the benefit of volunteerism. The medical, physical and social risks are minimal for all participants and are small in relation to the anticipated benefits of the knowledge to be gained. Additionally, the information that is obtained will be disseminated as widely as possible, including through submission for publication in peer-reviewed journals, presented at scientific conferences, and the many dissemination channels of the NIDDK and academic institutions involved. The results of this study may provide data for future studies that will lead to interventions that influence the development, management, and long-term outcomes for pediatric and adult study participants with USD. It is also possible that the information obtained because of this project will be used to develop clinical practice guidelines, which could directly benefit patients with USD in the future.

3 OBJECTIVES AND PURPOSE

The primary aim of the study is to determine whether a multi-component program of behavioral interventions to increase fluid intake will result in reduced risk of stone disease progression over a 2-year period. Under this aim, the study will test the following specific hypotheses, comparing 1) intervention arm: individuals participating in a multi-component program of behavioral interventions targeting increased fluid intake (sufficient to achieve a urine output $\geq$ 2.5 L daily or $\geq$ 30 mL/kg/day for those study participants aged < 18 years and weighing <75kg); versus 2) control arm: individuals receiving usual care:

a. **Primary hypothesis**: Participants in the intervention arm will have a reduced risk of symptomatic stones over 2 years.
b. **Secondary hypothesis #1:** Participants in the intervention arm will have a reduced risk of stone disease progression (a composite outcome comprising symptomatic stone events, new asymptomatic stone on imaging, or stone growth of at least 2 mm on imaging) over 2 years.
c. **Secondary hypothesis #2**: Participants in the intervention arm will have a reduced risk of forming new asymptomatic renal stones over 2 years.
d. **Secondary hypothesis #3:** Fewer participants in the intervention arm will exhibit growth in existing renal stones of at least 2 mm on imaging over 2 years.
e. **Secondary hypothesis #4:** Participants in the intervention arm will be more likely to achieve goal 24-hour urine output.
f. **Secondary hypothesis #5:** Participants in the intervention arm will be more likely to develop lower urinary tract symptoms (LUTS).
g. **Secondary hypothesis #6:** Greater urine output will be associated with reduced risk of stone disease progression, controlling for medication use (time updated), disease severity and clinical characteristics (e.g., body mass index).

h. **Secondary hypothesis #7:** Participants with pre-existing LUTS will be less likely to achieve 24-hour urine output goals as compared to those without pre-existing LUTS.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a two arm randomized controlled trial that incorporates pragmatic features, an adaptable intervention, patient choice, and remote monitoring of fluid intake through a "smart" water bottle. The study period is 24 months and will enroll approximately 1642 participants. Randomization will be stratified within a clinical center by (adult vs. adolescent) and (first time vs. recurrent stone former). Intervention and control arm study participants will receive a smart water bottle that records daily fluid consumption, usual care including guideline-based recommendations of adequate fluid intake to decrease kidney stone recurrence, and periodic 24 hour urine collections.

Participants in the intervention arm will receive an individualized "fluid prescription", which will be the additional volume of fluid intake needed to maintain a urine output of at least 2.5 L/day for study participants aged at least 18 years (adults) or 30 mL/kg/day for study participants aged 12-17 years inclusive (adolescents) and weighing < 75 kg; this additional fluid will be consumed from the smart water bottle. The prescription will be determined by the following equation: Initial Fluid Prescription = 1.2 x (2.5L – median urine volume on all 24-hour urine collections in the 12 months prior to enrollment). The fluid prescription may be modified, as needed, based on the 24-hour urine volume measurement obtained approximately 2 weeks after randomization. To reduce risk of unblinding treating providers, adjustments to the fluid prescription will be communicated by the study coordinator. The intervention arm also includes a behavioral program that consists of financial incentives and structured problem solving (SPS) to maintain the recommended fluid intake. The intervention period can be divided into phases of "induction," "consolidation," "taper," and "maintenance." The induction phase comprises the first 6 months of the intervention, and will initially include eligibility for FI on 100% of days. During induction, the intensity of the intervention can be increased for those study participants who do not consistently meet daily fluid intake goals by adding structured problem solving (SPS) to help participants develop feasible solutions to overcoming personal barriers to maintaining the prescribed fluid intake. The consolidation phase comprises the second 6 months and enables some additional potential for SPS-based adaptation of the intervention, but the frequency of the financial incentives will be slightly lower. The taper phase will comprise months 13 – 18, during which SPS is withdrawn and financial incentives are fully tapered. In the final 6-month maintenance phase, participants will have access only to "low touch" and low cost interventions (e.g., text reminders) that the participant selected to help sustain new habits of fluid consumption.

Participants in the control arm will receive standard care instructions according to American Urological Association (AUA) guidelines to increase overall fluid consumption to achieve UOP of at least 2.5 L daily. They will also receive a "smart" water bottle with capability to self-monitor their fluid intake, though the use of the "smart" water bottle is optional in the control arm. Approximately 2 weeks after randomization, a 24-hour urine volume measurement will be obtained, to provide control arm

participants with initial feedback as to whether or not they are meeting the urine output goal (urine output ≥ 2.5 L daily or 30 mL/kg/day for those study participants <75kg aged less than 18 years). Participants in the control arm will not receive additional incentives, but will receive monetary compensation for completion of study activities (e.g., urine collections, study-related imaging, and study completion).

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINT

Symptomatic kidney stone recurrence. A symptomatic stone will be defined as any of the following:

1. Stone passage observed and/or captured by the study participant
2. Procedural intervention for symptomatic stone
3. Any procedural intervention for removal of asymptomatic renal or ureteral stone (See section 10.4.2 for analytic details)

4.2.2 SECONDARY ENDPOINTS

1. Asymptomatic formation of new stone detected by imaging
2. Increased size of existing stone by ≥ 2 mm in any dimension detected by imaging
3. Composite outcome: symptomatic stone recurrence, asymptomatic stone formation, increase of existing stone by ≥2 mm in any dimension detected by imaging
4. 24 hour urine total volume
5. Costs of study interventions and treatments for USD during the follow-up period
6. Presence of lower urinary tract symptoms (Comprehensive Assessment of Self-reported Urinary Symptoms)

4.2.3 EXPLORATORY ENDPOINTS

1. Change in stone volume as estimated by imaging
2. Change in body weight since study entry

4.3 RANDOMIZATION

Study participants will be randomized in a ratio of 1:1 to one of two parallel study groups, designated as “intervention” and “control”. Randomization will be stratified within a clinical center by (adult vs. adolescent) and (first time vs. recurrent stone former). Randomization will be conducted at the clinical center level in blocks of variable size to minimize potential confounders related to differences in site-based care practices. The randomization will be performed with the use of an internet-accessible integrated randomization module in the EDC system.

The randomization scheme will be generated by a statistician at SDRC. This statistician will not be a part of the analytic team for the study results, to minimize the possible introduction of bias into study results.

4.4 REQUIREMENT FOR LOW URINE VOLUME

Participants must have documented low urine volume to be eligible for the study. However, study investigators recognize that obtaining an accurate 24-hour urine volume poses challenges to efficient study recruitment given that participants will need to become oriented to the set-up and use of a smart water bottle.

We will accept for eligibility a 24-hour urine volume within the 12 months prior to the study visit. If more than one 24-hour urine specimen is available during that time period, then investigators will calculate the median volume of the available specimens; the median AND the most recent volume must be less than 2.0 L or 25 mL/kg if age < 18 and weight < 75 kg (adolescents ≥75 kg will follow the 2.0L urine volume threshold). Where possible, the investigators will also use conventional criteria (based on urine total creatinine) to assess if a urine specimen is an undercollection or overcollection. If no urine specimen during the 12 months prior to the day of screening is available, investigators will ask otherwise eligible participants to complete a 24-hour urine collection for volume, osmolality, and creatinine excretion.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

1. Aged ≥ 12 years
2. At least 1 symptomatic stone event (passage or procedural intervention) within 3 years prior to enrollment or a symptomatic stone event within 5 years if the patient also has new stone formation detected on imaging during the last 5 years. Symptomatic stone defined as any of the following:
    a. Stone passage
    b. Procedural intervention
    c. Radiographically or ultrasonographically confirmed stone with any of the following:
        i. Gross hematuria
        ii. Renal colic or atypical abdominal pain attributed to the stone, as determined by a treating provider
        iii. A clinical pattern of intermittent symptoms consistent with intermittent obstruction at the ureteropelvic junction, as determined by a treating provider
3. Low 24-hr urine volume
    a. ≥18 years old: <2.0 L/day
    b. <18 years old and weight <75kg: <25 ml/Kg/day (adolescents ≥75 kg will follow the 2.0L criteria)
4. Able to provide informed consent (parental permission for children)
5. Owning and willing to use a smartphone or other device (e.g., tablet) compatible with the study-provided wireless enabled “smart” water bottle

5.2 PARTICIPANT EXCLUSION CRITERIA

1. Spinal cord injury
2. Currently undergoing active treatment for cancer except basal cell skin cancer, or patients with a history of cancer who completed their initial therapy < 1 year before screening.
3. Known infectious (struvite), monogenic or other causes of stone disease for which therapies are likely to significantly alter course of stone disease
    a. Cystinuria
    b. Primary hyperoxaluria
    c. Primary xanthinuria
    d. Primary hyperparathyroidism
    e. Sarcoidosis
    f. Medullary sponge kidney
4. History or presence of hyponatremia (serum sodium <130 mmol/L) or hypo-osmolality (serum osmolality <275 mosm/kg)
5. Study participants with comorbidities that preclude high fluid intake or prior surgery precluding high fluid intake or leading to GI fluid losses
    a. History of or current Crohn's disease, ulcerative colitis, short gut syndrome (e.g. ileostomy, bowel bypass surgery to treat obesity, small bowel resection), chronic diarrhea, or GI tract ostomy.
    b. History of malabsorptive (e.g., Roux-en-Y gastric bypass) or restrictive (e.g., sleeve gastrectomy) bariatric surgery procedures
    c. Congestive heart failure
        i. NYHA class II or greater, and/or
        ii. Hospital admission in the past year for heart failure
    d. Lung disease with a home oxygen requirement
    e. Chronic kidney disease (eGFR <30 ml/min/1.7 m2 over a 3-month period)
        i. For adults (age ≥18), we will use the CKD-Epi equation which requires the measurement of serum creatinine only.
        ii. For children (age <18), we will use the bedside Schwartz (CKiD) formula.
    f. Nephrotic syndrome (>3.5 grams of protein per 24 hours)
    g. Cirrhosis with ascites
6. Women who are currently pregnant or planning pregnancy within 2 years
7. Renal transplant recipient
8. Bedridden study participants (ECOG ≥ 3)
9. Uncorrected anatomical obstruction of the urinary tract
10. History of recurrent urinary tract infections (> 3 UTI/year proven by urine culture)
11. Exclusions due to medication use:
    a. Chronic use of lithium
    b. Long-term glucocorticoid use (> 7.5 mg prednisone daily for > 30 days prior to enrollment)
    c. Intake of narcotic medication on a daily basis for >30 days prior to enrollment
    d. Supplemental Vitamin C (> 1 g daily)
12. Individuals with stones that have developed after the initiation of medications that are strongly associated with USD such as carbonic anhydrase inhibitors (acetazolamide, topiramate, zonisamide), high dose vitamin C (> 1 g daily), high dose calcium supplementation (> 1,200 mg daily) AND who have discontinued or plan to discontinue these medications.

13. Individuals with stones composed of medications that may crystallize in the urine (guaifenesin, sulfonamides, triamterene, and the protease inhibitors indinavir and nelfinavir) AND who have discontinued or plan to discontinue these medications.
    Note: Individuals who are on long-term medications that increase the risk of stone disease, who **cannot stop these medications due to other chronic conditions** (e.g., HIV) and who **may reduce their risk for stone recurrence through increased fluid intake**, will be eligible to participate in the trial. Examples of these medications include:
    a. Carbonic anhydrase inhibitors (acetazolamide, topiramate, zonisamide)
    b. Medications that may crystallize in the urine (guaifenesin, sulfonamides, triamterene, and the protease inhibitors indinavir and nelfinavir).
14. Study participants <2 yrs life expectancy
15. Non-English Speakers
16. History of Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)
17. Anatomical urologic abnormalities including ileal conduits, horseshoe kidney, megaureter or solitary kidney
18. Psychiatric conditions impairing compliance with the study
19. Vulnerable population (prisoner and/or cognitive impairment that the investigator feels will impact the study participant's ability to participate in the protocol)
20. Individual who will be unable to participate in the protocol in the judgment of the investigator

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Adolescent and adult study participants will primarily be recruited into the study via two routes: a) referrals from their primary urologist or nephrologist in the USDRN Clinical Centers (CC) ; and b) surveillance of appropriate study participants in the EMR. However recruitment via other routes such as advertisements and press releases is allowed. Eligible study participants may be contacted by phone, letter, email or secure EMR messaging prior to in-person recruitment. Their providers will be alerted about plans for recruitment, as appropriate. EMR filters may be implemented to alert study staff about potentially eligible study participants' upcoming routine clinic visits. At the initial contact with the participant, study staff will explain the study rationale and goals, as well as the requirements for participation. Interested participants may be provided with copies of the informed consent documents and eligibility questionnaires to review and complete. Informed consent and enrollment will be obtained by CC-based staff. Participation will be completely voluntary and will not affect the participant's clinical care. If adult study participants and adolescent study participants (with consent also provided by parents/caregivers of adolescent study participants) are interested in participating, USDRN CC PIs or their designated staff will consent the study participant and parents/caregivers for enrollment. All participants will receive modest compensation for the time spent on completion of study-related procedures.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Study participants may withdraw from study intervention or the entire study at any time during the study without prejudice. If a participant withdraws from study intervention, other study assessments will continue through the end of the study. The participant may be discontinued from study intervention at the discretion of the investigator if medically necessary or if any untoward effects occur. In addition, a study participant may be withdrawn by the investigator or the sponsor if the study participant violates the study plan or for administrative and/or other safety reason. Study coordinators will report reasons for study withdrawal in the EDC database.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

The investigator or designee will notify SDRC immediately when a study participant has been discontinued or withdrawn from study intervention because of an adverse experience. When a study participant discontinues or is withdrawn from the study before study completion, the participant will be asked to complete activities scheduled for the Month 24 study visit at the time of discontinuation. Any adverse experiences that are present at the time of discontinuation/withdrawal should be reported and followed up in accordance with the safety requirements outlined in Section 8 Assessment of Safety.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTIONS AND CONTROL DESCRIPTION

6.1.1 OVERVIEW

	Control	Intervention
Platform	Participants will be provided with a wireless-enabled “smart” water bottle. Participants will be allowed, but not required, to use or sync the water bottle with their mobile device	Wireless-enabled “smart” water bottle Participants must sync water bottle with their mobile device daily
Fluid Goal	Usual care (sufficient fluid intake to achieve UOP ≥ 2.5L per 24 hours or 30/ml/kg/day for participants <18 years and <75kg)	120% of baseline UOP deficit via the water bottle, with modification possible at Week 2; 24-hour urine volume check @ 2 weeks, 6 months, 12 months, and 18 months.

	Control	Intervention
	24-hour urine volume check @ 2 weeks, 6 months, 12 months, and 18 months.	

Behavioral Intervention Program	none	<u>Months 0-6 (Induction):</u>
		• Daily financial incentive for success at meeting fluid intake goal via water bottle (FI possible 100% of days)
		• Structured Problem Solving (SPS)
		  ○ Non-adherence trigger if fluid goal was achieved less than 80% of days over two weeks (i.e., >3 days where fluid goal was not met during 14 day period) for two 14-day assessment periods.
		• SPS "Booster" (intensified counseling)
		  ○ Non-adherence trigger if fluid goal was achieved less than 80% of days over two weeks (i.e., >3 days where fluid goal was not met during 14 day period) for two 14-day assessment periods following initial SPS.
		
		<u>Months 7 -12 (Consolidation)</u>:
		• Daily financial incentive for success at meeting fluid intake goal via water bottle possibility of receiving incentive for 80% of days [24] in 1 month period)
		• Structured Problem Solving (SPS)
		  ○ Non-adherence trigger if fluid goal was achieved less than 80% of days over two weeks (i.e., >3 days where fluid goal was not met during 14 day period) for two 14-day assessment periods.
		• SPS "Booster" (intensified counseling)
		  ○ Non-adherence trigger if fluid goal was achieved less than 80% of days over two weeks (i.e., >3 days where fluid goal was not met during 14 day period) for two 14-day assessment periods following initial SPS.
		<u>Months 13 – 18 (Tapering)</u>:
		• Taper daily financial incentive (75% of days at month 13 and 15% of days at month 18)
		• Self-selected/low touch intervention(s)
		  ○ Text/phone reminders
		  ○ Commitment contract
		  ○ Social intervention (e.g., team)
		<u>Months 19-24 (Maintenance):</u>
		• Self-selected/low touch intervention(s)
		  ○ Text/phone reminders

	Control	Intervention
		○ Commitment contract ○ Social intervention (e.g., team) ○ Feedback of adherence
Stone-directed pharmacological or urological care	Per primary stone treating provider	Per primary stone treating provider

6.1.2 FINANCIAL INCENTIVES

As described above**,** a substantial percentage of USD patients have persistently low fluid intake, despite evidence that low fluid intake promotes stone recurrence. Maintaining fluid intake sufficient to prevent USD is difficult because the short-term benefits of fluid intake are not apparent since symptomatic stone episodes commonly take place after months or years without symptoms. Financial incentives may help bridge the gap between the perceived benefits of daily fluid intake and the future benefit of preventing USD recurrence by offsetting present-bias (tendency to focus on the present and heavily discount the future) through regular, ongoing positive reinforcement.[36,37] The immediate reinforcement provided by financial incentives can focus attention on adherence to fluid intake recommendations. The repeated, small payoffs increase the attractiveness of the incentive by giving participants intermittent positive reinforcement and take advantage of present-bias in decision-making surrounding adherence. Additionally, we will incorporate messages that inform non-adherent study participants about their missed opportunity for a payout; future adherence is thus further encouraged by harnessing regret-aversion (the tendency to make decisions based on desire to avoid losses and regret).[36,38-40]

We will use financial incentives during the first 18 months of the study. Eligibility for these incentives will be calculated daily (although, as noted elsewhere, incentives will not be delivered to participants daily during later phases of the trial). These incentives will be structured as a “loss” incentive, which has been shown to produce the greatest sustained improvement in health behaviors compared to other incentive delivery structures.[41] Each participant will be credited $1.50 for each day for which financial incentives are available. The participant will keep the $1.50 if they met or exceeded the prescribed fluid volume for that day and will forfeit the $1.50 if he/she did does not meet the goal. The intervention period will be divided into 6 month phases of “induction”, “consolidation”, “taper”, and “maintenance.” The utilization and frequency of financial incentives will vary across these periods.

At the start of each month in the trial, each participant will be credited with funds in their Way to Health account corresponding to the total possible rewards available during that month (described below) in the event of meeting fluid intake goals each day. The funds credited to the participant’s account that month (and total earnings since starting the trial) can be tracked by each participant easily through his or her Way to Health account. Participants will receive a distribution of funds from their account approximately every 4 weeks.

Induction (months 1-6): Financial incentives available for 100% of days

Consolidation (months 7-12): Financial incentive available for 80% of days during the study period, i.e. twenty-four days during a 30 day month during this phase will be randomly assigned to have a financial incentive available.

Taper (months 13-18): Decrease in the frequency of financial incentives

Month 13: 75% of days (22)

Month 14: 65% of days (19)

Month 15: 50% of days (15)

Month 16: 35% of days (10)

Month 17: 25% of days (7)

Month 18: 15% of days (4)

Maintenance (months 19-24): no financial incentives

In order to be eligible for the financial incentive, the participant must:

1) Drink a minimum of the prescribed fluid volume from the smart water bottle
2) Sync the water bottle to their mobile device as instructed

The participants will receive the following feedback through their choice of text message, email, or a combination thereof.

Feedback messages will leverage the principle of loss aversion by reminding study participants that money in their account was retained or lost depending on their fluid intake. Participants should be motivated to prevent further losses on subsequent days. Details on the messaging that participants may receive are included in the Way to Health MOP.

6.1.3 STRUCTURED PROBLEM SOLVING

Structured Problem Solving (SPS) is well suited to the substantial challenges of sustaining adequate fluid intake, which requires tailoring the advice and encouragement to each patient's needs. For example, each PUSH trial participant will have different schedules (some individuals may spend most of the day outside the house, requiring them to carry a bottle with them), health literacy, health conditions (such as urinary incontinence), and social support that must be addressed to change their fluid intake. Behavior change also requires repeated feedback, which SPS is inherently structured to provide. The SPS approach can meet the challenge of helping PUSH study participants identify feasible solutions to overcome these diverse barriers to increase fluid intake.

Participants assigned to the intervention arm who do not meet the daily fluid goal for ≥80% of days (11) over two 14-day periods during months 1-12 will receive SPS to identify their individual, specific barriers

to fluid intake and develop a systematic approach to learn how to overcome these barriers.

A health coach with specific expertise or specifically trained by an expert for this role will administer SPS. Participants randomized to the intervention arm who meet criteria for receiving SPS will meet with the health coach initially for approximately 30 minutes. This meeting could take place in person, over the phone, or virtually through audiovisual media. The introductory session will consist of education concerning the prescribed fluid intake regimen, adherence expectations, and any fluid intake misperceptions, as outlined in the SPS Manual of Procedures. There will be scheduled follow-up feedback sessions to review the prior participant's daily fluid intake and allow for problem solving of new issues. Participants will also receive daily, automated feedback of their fluid intake via Way to Health (based on smart bottle data).

The coach will record root causes of fluid intake below goal and identify successful approaches used to address the major barrier(s). During months 1-12, participants who have received SPS, but still have fluid adherence < 80% of days over two 14-day assessment periods (i.e., >3 days where fluid goal was not met during 14-day period), will receive up to 2 "booster" sessions, which will consist of intenstified counseling and root cause analysis and remediation of reasons for lack of adherence. Booster SPS sessions may be delivered in person or remotely (audio/video or audio-only interface), in accordance with the SPS MOP.

If, after 2 booster sessions, adherence is still below 80% for subsequent assessment periods, the participant will be offered the opportunity to select one or more "low touch" interventions (e.g. automated fluid intake reminders from HidrateSpark) to continue throughout the remainder of the study period. The rationale is that application of an intensive intervention that has not resulted in behavior change will be unlikely to do so with continued application and may decrease participant retention. Regardless of whether the participant in the intervention arm has received SPS, he/she will continue to be eligible for financial incentives according the the schedule described in Section 6.1.2.

The health coach will undergo structured training to gain expertise in the specific nutritional needs of study participants and strategies to improve adherence. Health coaches will use the Way to Health platform to review fluid intake and urine volume and have meetings to share advice about how to achieve the fluid intake goals.

Additionally, SPS-based communications between the health coach and participants will be logged in the EDC database.

6.2 STRUCTURED PROBLEM SOLVING FIDELITY PROCEDURES

The initial SPS sessions (in person or remote using audio-visual media) will be digitally recorded (audio only) and a random sample from each USDRN-CC will be reviewed to assess the fidelity of the facilitator to the intervention, as outlined in the Manual of Procedures.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY-SPECIFIC PROCEDURES

Study participants will undergo laboratory and imaging evaluations at specified intervals during the study period (see Schedule of Events, 7.3).

Screening

At screening, participants will complete serum chemistry, serum osmolality, 24-hour urine creatinine, 24-hour urine total volume, 24-hour urine osmolality, and review of medical history, medications, and demographic information.

In place of new testing at screening, we will accept for eligibility:

- Blood laboratory results within 18 months prior to the screening visit, provided that the participant does not meet any of these risk criteria for hyponatremia:
    - Age 65 or older
    - Taking thiazide diuretics
    - Taking SSRI medications
    - Last eGFR 30 – 45 mL/min/1.73 m2

  If a participant has completed a blood metabolic panel in the 30 days prior to screening, those results can be used to assess blood sodium levels and the participant's risk for hyponatremia.

- A 24-hour urine collection within the 12 months prior to the screening visit. If more than one 24-hour urine specimen is available during that time period, then investigators will calculate the median volume of the available specimens; the median value AND the most recent volume must be less than 2.0 L or 25 mL/kg if age < 18 and weight < 75 kg (adolescents ≥75 kg will follow the 2.0L criteria).

  If a participant completed one or more 24 hour urine tests in the 12 months prior to screening and the 24-hour urine panel was run, the results of the most recent panel will be accepted in place of a new collection provided that the following were obtained:

    - Total Volume
    - Creatinine
    - Citrate
    - pH
    - Sodium
    - Uric acid

- Oxalate
- Calcium

If the results listed were not obtained, study participants will undergo a new screening 24-hour collection and the full urine panel.

Baseline

At the baseline visit study participants will have their weight and height recorded and undergo baseline imaging (low dose CT for participants aged ≥ 18 years, renal ultrasound for those aged < 18 years at enrollment; imaging details in Manual of Procedures). Adult females (ages 18 years and older) of childbearing potential will undergo a pregnancy test (urine HCG) prior to their baseline imaging.

In place of new imaging at baseline, we will accept:

- Stone protocol CT scans (for adult participants) performed in the 3 months prior to the baseline visit, or
- Renal ultrasound (if age <18) performed in the 3 months prior to the baseline visit

Provided that

- They are reviewed by the Investigator and deemed comparable to the imaging that would have been completed at baseline, with views in 3 dimensions.
- The participant has not had a stone passage event or removal procedure since the completion of the scan.

In order to facilitate recruitment, the Baseline imaging, and the associated pregnancy test for adult females, may be waived for participants:

- Enrolled and randomized from locations other than the 6 primary Clinical Centers/study sites
- Enrolled from an existing Clinical Center/site, but who are otherwise eligible but are refusing participation in the study because of imaging

The waiver of imaging will be documented in the study database. Adult female participants will be asked to verbally confirm that they are not pregnant or planning to become pregnant during their time in study.

All participants will be randomized to either the intervention arm or the control arm. Participants in the intervention arm will receive a smart water bottle, and will create accounts with Hidrate Spark, Way to Health, and in the EDC database, and will receive their initial fluid prescription. Participants in the control arm will receive the smart water bottle but will not be required to create a Hidrate Spark account; they will however be required to create Way to Health and EDC database accounts.

Note: The screening and baseline visits may be combined into a single, in-person visit, provided that:

1. Informed consent is obtained from the participant prior to any study procedures or collection of data in the EDC database.
2. Participant eligibility must be confirmed by the Investigator prior to randomization.

2 Weeks After Randomization

At 2 weeks (± 7 days) post-randomization, participants in intervention and control arms will complete a 24 hour urine collection, include volume and panel. In the intervention arm, this 24 hour urine total volume may be used to adjust the initial fluid prescription. In the control arm, study participants will be notified that their 24-hour urine total volume is at or above the target volume (2500 mL/24 hours or 30 mL/kg for those study participants <75kg aged less than 18 years) or below the target volume, and advised about their fluid intake in accordance with guideline-based recommendations of adequate fluid intake.

Follow-Up Procedures

All study participants will receive emails from the EDC database prompting them to log in to their account (which they created at baseline) and complete the follow-up visit questionnaire at months 3, 6, 9, 12, 15, 18, 21, and 24. As a part of the questionnaire, they will be asked to provide their current weight and height, and answer questions pertaining to their stone disease. Adult participants will be prompted to also complete the lower urinary tract symptoms questionnaire (the CASUS) at 6, 12, 18 and 24 months.

All study participants will undergo follow-up imaging at 24 months (low dose CT for participants aged≥ 18 years at enrollment, renal ultrasound for those aged < 18 years at enrollment; imaging procedure details in Manual of Procedures). Adult females (ages 18 years and older) of childbearing potential will undergo a pregnancy test (urine HCG) at month 24 prior to the CT scan.

In place of new imaging at Month 24, we will accept:

- Stone protocol CT scans (for adult participants) performed in the ±60 day window for the Month 24 visit, or
- Renal ultrasound (if age <18) performed in the ±60 day window for the Month 24 visit

Provided that

- They are reviewed by the Investigator and deemed comparable to the imaging that would have been completed at Month 24, with views in 3 dimensions.
- The participant has not had a stone passage event or removal procedure since the completion of the scan.

In order to facilitate recruitment, the Month 24 imaging, and the associated pregnancy test for adult females, may be waived for participants:

- Enrolled and randomized from locations other than the 6 primary Clinical Centers/study sites
- Enrolled from an existing Clinical Center/site, but who are otherwise eligible but are refusing participation in the study because of imaging

The waiver of imaging will be documented in the study database.

In addition, at 6, 12, 18 and 24 months, participants will undergo 24-hour urine total volume, 24-hour urine creatinine, and 24-hour urine osmolality assessment. If a participant completed a 24 hour urine test within the ±30 day window for the Month 6, 12, 18 and within the ±60 day window for the Month 24 visit, the results of the most recent panel will be accepted in place of a new collection provided that the following were obtained:

At Months 6, 12, 18:

- Total Volume
- Creatinine

At Month 24:

- Total Volume
- Creatinine
- Citrate
- pH
- Sodium
- Uric acid
- Oxalate
- Calcium
- Phosphate

A 24-hour urine panel will also be performed at Month 24, although results of this test will not be available to the DSMB until study conclusion.

Adolesecents who turn 18 years old during the study will continue to perform the adolescent procedures (no LUTS questionnaire, ultrasound scans in place of CT) so that their data is comparable throughout their participation.

7.1.3 STANDARD OF CARE STUDY PROCEDURES

Current guidelines recommend annual imaging to detect asymptomatic stone activity (formation or growth) for individuals with urinary stone disease. Study participants may undergo low dose CT scan (renal ultrasound for study participants age < 18 years at enrollment) at 12 months as part of standard

of care monitoring for their urinary stone disease, or as a part of a surgical procedure to remove a stone. Results of these studies may be available through the treating physician. Data from other stone-directed imaging studies performed at the direction of the participant's treating physician at 12 (+/- 1) months and throughout the study follow-up period may also be collected.

7.1.4 BIOREPOSITORY SPECIMEN COLLECTION

In addition to study-specific laboratory tests, blood, urine and stone samples as well as stool samples will be obtained for use in future studies. These samples along with the study data (including digital imaging data) will be stored in the NIDDK Repositories, supported by the National Institutes of Health. These data and stored samples will be available to use in research for the study of USD after PUSH is complete.

Biospecimens collected as part of the study will include:

- Whole blood (DNA)
- Serum
- Plasma
- Urine
- Stool
- Kidney stone sample (if available)

7.1.5 DATA COLLECTION PROCESS

Study data from these sources will be integrated at the SDRC.

Clinical Centers/Sites: Clinical Center/site personnel will complete eCRFs (in the EDC database managed by the SDRC) during the study period covering participant eligibility and baseline information, outcome events, study procedures (other than 24 hour urine collection), and safety monitoring (see Section 8).

Way to Health: The study will leverage the NIH-funded Way to Health web-based platform at the University of Pennsylvania (UPENN) (RC2-AG036592-01). This platform for clinical trials implementation provides a secure, efficient, user-friendly approach to monitoring participation, delivering feedback/communications (*e.g.*, through emails, texts or phone messages using Automated Interactive Voice Response) and incentives in an automated fashion. All USDRN CCs will leverage the existing Way to Health infrastructure through administration of financial incentives and collection of fluid consumption data in real-time. These data will be securely transmitted to SDRC periodically as specified in the PUSH Manual of Procedures and the SDRC/WTH Data Transfer Agreement.

Hidrate Spark: Data regarding participants' daily fluid intake will be securely transmitted to Way to Health on a daily basis. All participants in the intervention arm will have their data transferred. Only participants in the control arm who choose to set-up their smart water bottle will have data transmitted.

Core Lab: 24-hour urine collections will be processed at a core lab facility for the USDRN, located at University of Texas Southwestern. Results will be securely transmitted to SDRC periodically as specified in the PUSH Manual of Procedures and the SDRC/UTSW Data Transfer Agreement.

All data and records generated during this study will be kept confidential in accordance with Institutional policies and Health Insurance Portability and Accountability Act (HIPAA) on study participant privacy. Investigators and other site personnel will not use such data and records for any purpose other than conducting authorized research. IRB approvals will be obtained prior to initiating study activities.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Study participants will complete periodic clinical laboratory evaluations, as outlined in the Schedule of Events Table (7.3).

These will include 24-hour urine volume, 24-hour urine analysis (calcium, creatinine, citrate, phosphorous, pH, sodium, urea nitrogen, oxalate, chloride, ammonium, magnesium, potassium, uric acid, sulfate, qualitative cystine[baseline]) and 24-hour urine osmolality. Supersaturations of calcium oxalate, calcium phosphate and uric acid will also be included. Urine Hcg will be performed on adult females of childbearing potential in association with CT scans, only; when a waiver of imgaging is granted, this testing is also waived. Serum chemistry and osmolality will be obtained on participants without recent test results.

7.2.2 OTHER ASSAYS OR PROCEDURES

Study participants will undergo baseline and end-of-study imaging (low dose CT for participants aged ≥ 18 years, renal ultrasound for those aged < 18 years at enrollment; imaging procedure details in Manual of Procedures) during the study, as outlined in the Schedule of Events Table (7.3). Historical records will be accepted in place of the baseline CT scan, as explained in Section 7.1.1. Waivers of imaging will be allowed, as explained in Section 7.1.1.

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Specimen preparation, handling and storage will be in accordance with the PUSH Manual of Procedures and the clinical centers' institutional procedures.

7.2.4 SPECIMEN SHIPMENT

Specimen shipment for study specimens and specimens collected for the NIDDK Repository shall be shipped according to the procedures outlined in the PUSH Manual of Procedures.

7.3 SCHEDULE OF EVENTS TABLE

Procedure	Screen	Baseline	2 weeks ± 7 days	3 mos ± 30 days	6 mos ± 30 days	9 mos ± 30 days	12 mos ± 30 days	15 mos ± 30 days	18 mos ± 30 days	21 mos ± 30 days	24 mos ± 60 days
Informed Consent	X										
Email/Telephone Follow Up				X	X	X	X	X	X	X	X
Serum chemistry/eGFR	X										
Serum osmolality	X										
Hcg (urine dip)α		X									X
Randomization		X									
Provide smart water bottle*		X									
24-hour urine panel†	X†		X†								X
24-hour urine TV	X‡		X		X°		X°		X°		X°°
24-hour urine Cr	X‡		X		X°		X°		X°		X°°
24-hour urine osm	X‡		X		X°		X°		X°		X°°
Imagingα		X					X§				X~
Medical History	X										X
Weight and Height		X		X	X	X	X	X	X	X	X
LUTS assessment‖		X			X		X		X		X

* All participants are provided with a smart water bottle, but only participants randomized to the intervention arm are required to set-up the bottle and use it during the study.

†24-hour urine panel includes: calcium, creatinine, citrate, phosphorous, pH, sodium, urea nitrogen, oxalate, chloride, ammonium, magnesium, potassium, uric acid, sulfate, qualitative cystine. Qualitative cystine will only be performed for Week 2 collection. A Screening/Baseline 24 hour urine panel will only be done if the participant does not have the historical panel results needed for determining eligibility (see Section 7.1.1).

‡A single 24-hour urine sample will be collected at screening for participants without any 24-hour urine tests in the 12 months prior to the Screening visit and the central lab will run urine volume, creatinine and osmolality only on this sample. For participant with prior 24-hour urine tests but without the results listed in Section 7.1.1, a new sample will be collected at screening and the full panel will be run on this sample.

° For Months 6, 12, 18, a clinical 24 hr urine can be used in place of a new collection provided it is within the ±30 day window of that visit and it includes volume and creatinine.

°° For Month 24, a clinical 24 hr urine can be used in place of a new collection provided it is within the ±60 day window of that visit and it includes the results listed in Section 7.1.1.

α Imaging at Baseline and Month 24, and the associated pregnancy testing for adult females, may be waived for participants enrolled from locations other than the primary Clinical Centers/sites, or who are enrolled from an existing CC and qualify but are declining participation in the study because of imaging. Adult female participants will be asked to verbally confirm that they are not pregnant or planning to become pregnant during their time in study.
§ Imaging = low dose CT (adults); renal u/s (adolescents); imaging at 12 months considered standard of care procedure and not required. SOC imaging done at any point during the participant's follow-up will be collected and entered in the EDC database.
~ For Month 24, imaging performed for clinical care can be used in place of new imaging provided it was completed within ± 60 days of the visit, and the criteria in Section 7.1.1 are met.
‖ Assessment of Lower Urinary Tract Symptoms in study participants aged ≥18 years using Comprehensive Assessment of Self-Reported Urinary Symptoms (CASUS)

7.4 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

Participants in both arms will continue to receive clinical care from their treating urologist and/or nephrologist. Study participants will not be permitted to enroll in other trials of novel therapeutics to prevent or treat urinary stone disease.

Medications that reduce kidney stone recurrence are permitted in both arms. These medications include:

1) sodium or potassium citrate
2) thiazide diuretic
3) allopurinol

Any surgical procedure for treatment of a kidney stone is permitted. These procedures include:

1) ureteroscopy
2) shock wave lithotripsy
3) percutaneous nephrolithotomy

An outcome adjudication committee will adjudicate all procedures performed to determine if they were performed for a symptomatic stone, which is the primary outcome measure.

7.4.1. CHANGES IN PARTICIPANT CLINICAL STATUS OR TREATMENT DURING THE TRIAL

Analyses will adhere to an intention to treat principle, such that every attempt will be made to collect outcome information on all participants (even if the participant is unwilling or unable to adhere to the assigned intervention). It is possible that some participants may start new clinical regimens or develop new clinical conditions during the trial that were contraindications to enrollment. The following characteristics or treatments would require cessation of the intervention:

Incarceration, hyponatremia requiring medical intervention, and/or any condition preventing high fluid intake such as advanced CHF or cirrhosis with ascites.

The following characteristics or treatments would not require cessation of the intervention, but should be recorded by the study staff:

Study participants who develop struvite stones, cystine stones, or who started lithium use, diuretic use, topiramate use, ketogenic diet, chronic corticosteroid use, supplemental vitamin C; or develop recurrent UTIs.

Study participants who become pregnant during the study will be removed from the study with their pregnancy followed until final outcome (as described in 8.4.5).

7.5 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

The following medications, treatments, and procedures are prohibited at screening, and should result in a potential participant being deemed a screen failure:

1) Lithium use
2) Loop diuretic use
3) Interventions and medications that cause stones
    a. Chronic corticosteroid use (>1 month)
    b. Supplemental Vitamin C (>1 g daily)
4) Novel therapeutics for stone prevention

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

Participation in the proposed study is completely voluntary. The research team will institute strict procedures to maintain confidentiality. All data and records generated during this study will be kept confidential and in accordance with institutional policies and HIPAA privacy policies. Study participants will be assigned a unique identification code that will be used as the sole identifier. Study participants and families will have direct access to the study team as a means to voice any questions, concerns, or reservations. Contact information will be provided at the time of consent. Should any specific concerns arise, the study team will intervene to address problems including, if needed, a change or discontinuation of study procedures. The appropriate institutional IRBs and DSMB will be informed of serious adverse events or protocol deviations, as outlined below.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse Event

An adverse event (AE) is any untoward medical occurrence associated with the use of a study intervention in a study participant. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product or biologic. Diseases, signs, symptoms, or laboratory abnormalities already existing at the time of consent are not considered AEs unless they worsen (i.e., increase in intensity or frequency). Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Surgical procedures planned before randomization and the conditions leading to these measures are not AEs.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious Adverse Event

An AE or SAE is considered serious if the investigator believes any of the following outcomes may occur:

1. Death.

2. Life-threatening AE: places the study participant, in the view of the investigator, at immediate risk of death at the time of the event as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death.

3. Persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions.

4. Congenital abnormality or birth defect.

5. Requires inpatient hospitalization or prolongation of existing hospitalization with the following exceptions:

    - Preplanned (before the study) hospital admissions, unless the hospitalization is prolonged

    - Planned admissions (as part of a study)

    - Rehospitalizations (after discharge from index hospitalization) of less than 24 hours

    - Elective procedures

    - Emergency department visits

Important medical events that may not result in death, be life threatening, or require inpatient hospitalization may be considered a serious adverse event (SAE) when, based on appropriate medical judgment, they may jeopardize the study participant and/or require medical or surgical intervention to prevent one of the serious outcomes listed above. This determination is based on the opinion of the Investigator.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems are any event that is: unexpected in nature, frequency or severity; related or possibly related to participation in the research; or suggest that the risk of harm to study participants is increased.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 ASSESSMENT OF ADVERSE EVENT SEVERITY

The determination of AE severity rests on medical judgment of a medically qualified investigator. The severity of AEs will be graded using the following definitions:

- **Mild**: Awareness of sign, symptom, or event, but easily tolerated.
- **Moderate**: Discomfort enough to cause interference with usual activity and may warrant intervention.

- **Severe**: Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention.

8.2.3 EXPECTEDNESS

Any adverse event, the specificity, nature, or severity of which is not consistent with the underlying disease process, will be considered an unexpected AE. AEs that are expected based on the underlying disease process are worsening renal function, ureteral stricture disease, or obstructed urinary infection.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The site Investigator is responsible for monitoring the safety of participants enrolled into the study at the study sites. Monitoring for AEs and SAEs will occur from informed consent to month 24. Adverse events will be queried as part of periodic email/telephone follow-up with participants.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

For this study, non-serious AEs will not be collected on the safety reporting page of the eCRF, but should be documented in the source documents and followed according to local standard of care. Investigators are also responsible for promptly reporting AEs to their reviewing IRB in accordance with local requirements.

8.4.2 SERIOUS ADVERSE EVENTS

SAEs occurring from *informed consent* to month 24 will be captured on the SAE eCRF.

8.4.3 SERIOUS ADVERSE EVENT REPORTING

All SAEs, whether or not deemed intervention related or expected, must be reported by the investigator or qualified designee within 1 working day of first becoming aware of the event. The investigator or qualified designee will enter the required information regarding the SAE into the appropriate module of the eCRF. If the eCRF system is temporarily unavailable, the event, including the investigator-determined causality to study intervention should be reported via the back-up paper SAE form to the SDRC. Upon return of the availability of the electronic data capture (EDC) system, the SAE information must be entered into the eCRF.

When additional relevant information (i.e., final diagnosis, outcome, results of specific investigations, etc.) becomes available, the Investigator will record follow-up information according to the same process used for reporting the initial event as described above. The Investigator will follow all reportable events until resolution, stabilization or the event is otherwise explained.

The SDRC will follow all SAEs until resolution, until stabilization, until otherwise explained or until the last subject completes the final follow-up, whichever occurs first. The SDRC will report all SAEs to the Data Safety Monitoring Board (DSMB) chair in accordance with the DSMB Charter.

8.4.4 UNANTICIPATED PROBLEM REPORTING

AEs that meet the criteria of serious, related to study intervention, and unexpected, qualify for expedited reporting to the IRB. The Investigator will assess all SAEs occurring at his/her clinical center and evaluate for "unexpectedness" and relationship to study procedures or intervention. The Investigator is required to complete and submit a report for the events identified as serious, study procedure or intervention related, and unexpected and submit the report to their reviewing IRB in accordance with local requirements.

A copy of this report should be kept at the clinical center and also forwarded to the SDRC within the same timeline used for reporting to regulatory authorities.

8.4.5 EVENTS OF SPECIAL INTEREST

Episodes of hyponatremia requiring medical attention (e.g., hospitalization) will be reported as a Serious Adverse Event, as described in 8.4.2.

8.4.6 REPORTING OF PREGNANCY

During the course of the trial, all study participants of childbearing potential will be instructed to contact their Investigator immediately if they become pregnant. Pregnancy occurring during the study period, although not considered a serious adverse event, must be reported within the same timelines as a Serious Adverse Event. The pregnancy will be recorded on the appropriate pregnancy form in the EDC database. The pregnancy will be followed until final outcome. Any associated AEs or SAEs that occur will be recorded in the EDC database.

8.5 SAFETY OVERSIGHT

The Investigator is responsible for monitoring the safety of participants enrolled into the study at their clinical center. The SDRC will follow all SAEs until resolution, until stabilization, until otherwise explained or until the last subject completes the final follow-up, whichever occurs first. The SDRC will report all SAEs to the Data Safety Monitoring Board (DSMB) chair in accordance with the DSMB Charter.

The DSMB will review detailed safety data approximately every 6 months throughout the study.

9 CLINICAL MONITORING

SDRC will employ a "risk-based monitoring" strategy that ensures human subject protection and data quality are held in the utmost regard. Data-Driven Trial Management (DDTM) is a targeted analysis–based surveillance effort designed to proactively minimize risk and improve quality.

SDRC focuses on a simple and pragmatic project management strategy based on the following quality by design principles with human subject protection and data quality and integrity as the foundation of project planning and execution: 1) the correct subjects are enrolled and consented, 2) acceptable treatment adherence is met, 3) complete efficacy data is ascertained, 4) complete safety data is ascertained, and 5) good clinical practices (GCP) are followed.

Integrated SDRC systems support our RBM strategies allowing us to closely monitor and track agreed upon key risk indicators and follow-up quickly with necessary interventions. In addition, our systems support focused monitoring activities, including source data verification, online drug accountability, and regulatory document tracking.

Based on our significant data quality experience, the SDRC has established strategies and supporting tools to deliver high quality data that is critical for all trials including long term, event driven trials. By integrating the varied data sources and providing seamless reporting of trial data status, we enable the team to proactively manage trials.

As part of a concerted effort to follow the study in a detailed and orderly manner in accordance with established principles of GCP and applicable regulations, a SDRC team member will maintain frequent telephone and written communication.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

The statistical team at SDRC will perform the statistical analyses described in this section. An Intention-to-treat analysis will be performed and will serve as the primary analysis for the primary objective in this study. The Intention-to-treat cohort will include all randomized study participants.

In a separate document, a statistical analysis plan (SAP) will be developed by the SDRC team to include a comprehensive description of the statistical methods and analyses for the primary manuscript as well as the final study report. Prior to analysis, study population details, including the number of sites, the number of study participants in each study arm, and the number of study participants lost to follow-up will be described. Data for all randomized study participants, whether or not they completed all protocol requirements, will be included for analysis.

10.2 STATISTICAL HYPOTHESES

The primary hypothesis of the time-to-first symptomatic stone will be tested under Cox proportional hazards model as:

$$\mathrm{H}_0\colon \mathrm{HR} = 1.0 \;\; vs. \;\; \mathrm{H}_a\colon \; \mathrm{HR} \neq 1.0$$

Other hypotheses of interest that the intervention will increase fluid intake (goal urine output at least 2.5 L daily) will lead to a fewer symptomatic and asymptomatic stone events over 2 years of study period. In addition, we will test time-to-recurrent symptomatic stone events.

10.3 ANALYSIS DATASETS

Data from all randomized study participants, regardless of whether or not they completed all protocol follow-up requirements, will be included for analysis. The analysis population will be the intent-to-treat (ITT) population. In addition, a per-protocol analysis will be performed. The analysis population for the per protocol analysis will consist of partcipants in the ITT population except those who have had a major protocol deviation.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

The primary analysis will be conducted by intention-to-treat principles. The analysis cohort for this study consists of all randomized study participants regardless of whether the study participant received the randomly assigned intervention strategy. All study participants who provide informed consent and who are randomized will be included in the analyses. For those study participants who are lost to follow-up, or who drop out of the study, the analyses will include all data up to the point of their last data collection whenever applicable. Safety data will be collected on all randomized study participants. All statistical analysis will be tested at two-sided nominal significance level of 0.05. If missing data constitute <2% of observations, the analysis will utilize single imputation (mean for continuous variables, mode for categorical variables). If missing data are >2% of observations, then the approach to missing data will depend on checks of the missing-at-random assumption, and will be detailed in the Statistical Analysis Plan.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint (symptomatic stone event) will be analyzed as a time-to-event outcome with a log-rank test[42] or equivalently, the Cox proportional hazards model,[43] the approach used for calculating sample size requirements. Kaplan-Meier estimates[44] of cumulative event rates as a function of follow-up time will calculated and displayed. In addition, stratified Cox proportional hazards model will be conducted where the strata are those used in the randomization scheme. Furthermore, data collected on subsequent recurrent events of symptomatic stone will be analyzed using the Andersen-Gill model[45] (with adjustment for correlation within a study participant) and/or negative binomial regression.

A symptomatic stone event will be defined as stone passage, symptomatic stone requiring procedural intervention, or any asymptomatic stone undergoing procedural intervention. A pre-specified sensitivity analysis of the definition of symptomatic stone event will include stone passage, symptomatic stones requiring procedural intervention, and asymptomatic stones undergoing procedural intervention that meet at least one of the following criteria: stone size at least 4 mm in any dimension, mobile stone, hematuria or recurrent urinary tract infection. An additional pre-specified sensitivity analysis will exclude any symptomatic stone events that occur within 30 days of randomization.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints will include a composite outcome of symptomatic stone event, asymptomatic stone formation, or stone growth assessed at study conclusion. These outcomes will be analyzed using a logistic regression model, since asymptomatic stone formation or stone growth are subject to interval censoring (the exact occurrence time will be unknown).

24 hour urine total volume and lower urinary tract symptoms (as measured by CASUS) will be compared between intervention and control arms using t-test or Wilcoxon rank-sum test, based on the assumption of normality of the data.

10.4.4 SAFETY ANALYSES

Proportion of study participants developing symptomatic hyponatremia will be compared in the intervention and control arms using the Pearson's chi square test or Fisher's exact test, as appropriate.

10.4.5 ADHERENCE AND RETENTION ANALYSES

24-hour urine total volumes will be the main adherence outcome.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Baseline descriptive characteristics will include demographic (age, race/ethnicity, sex), socioeconomic status, body mass index, stone former status (first time vs recurrent), baseline medication use, and 24-hour urine volume at study entry. Baseline characteristics will be summarized as mean (standard deviation), median (25^{th}, 75^{th} percentiles), min and max.

10.4.7 PLANNED INTERIM ANALYSES

Interim efficacy analyses are not planned. However, the study leadership will monitor the data integrity and sample size assumptions while the study is ongoing at two time points: 1) when approximately 1/3 of the study participants are enrolled or 12 months after the 1^{st} study participant enrolled, whichever occurs first; and 2) when about 2/3 of the study participants are enrolled or 20 months after the 1^{st} study participant enrolled, whichever occurs first.

The event rate and dropout rate will be monitored in an aggregated fashion (ie, blinded to the intervention allocation). If the event rate is lower than anticipated, or if dropouts exceed the assumed

rate, then the target enrollment might be increased to maintain sufficient power to complete the study. In addition, if study enrollment is slower than expected, additional recruitment sites may be identified.

The fidelity of SPS will be assessed in two ways. First, health coaches and participants will complete separate checklists noting which elements of SPS were addressed during the session(s). Second, a 15% random sample of SPS sessions will be audio or video recorded and assessed by independent reviewers for adherence to the specified elements of SPS.

10.4.7.1 DATA AND SAFETY MONITORING REVIEW

A Data and Safety Monitoring Board (DSMB) will be appointed by the NIDDK to monitor study participant safety and to review performance of the protocol. A DSMB Charter that outlines the operating guidelines for the committee and the procedures for the interim evaluations of study data will be developed by the NIDDK and agreed upon at the initial meeting of the DSMB. Reports will be prepared regularly by the SDRC as requested by the DSMB chair. Depending upon the operational plan established by the DSMB, the report might include recruitment and retention rates, interim analyses, primary and secondary endpoints, SPS fidelity, adherence, and other information as requested by the committee. After each meeting, the DSMB will make recommendations to the NIDDK and the trial leadership about the continuation of the study.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

Subgroup analyses will be performed for the primary outcome among the ITT population in order to explore whether intervention on symptomatic kidney stone are consistent across subgroups. The same subgroup analyses will also be repeated in the per-protocol population. Subgroups of interest would be clinical centers, sex, race, age (adult/adolescent), baseline medical treatment for USD prevention and first time/recurrent stone former. An SPS treatment fidelity subgroup analysis may be conducted, if sufficient variability in fidelity exists. Subgroup analyses will be summarized in a forest plot which will include the interaction p-values.

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

A single primary outcome is specified, therefore no adjustment for multiple primary endpoint comparisons will be necessary. Secondary outcome comparisons will not be adjusted for multiple testing.

10.4.10 ECONOMIC ANALYSIS

In accordance with expert recommendations, the economic evaluation will be performed using the societal perspective.[46] Using data already being collected during the trial, the following economic model inputs will be estimated: (1) resources required to provide the study interventions; (2) patient time and (3) medical resource use. To estimate study intervention costs, we will use a tool specifically designed to estimate costs associated with patient-centered interventions (R01NR011873).[47] The costs of medical resource use will be assigned based on payment schedules (e.g., Medicare). To incorporate potential differences in health-related quality of life experienced by participants in the cost-effectiveness analysis,

health state utilities will be estimated from existing literature.[48] Full details of the economic analysis will be specified in the Economic Statistical Analysis Plan. Cost effectiveness analyses will use estimates of incremental cost effectiveness ratios (ICER).

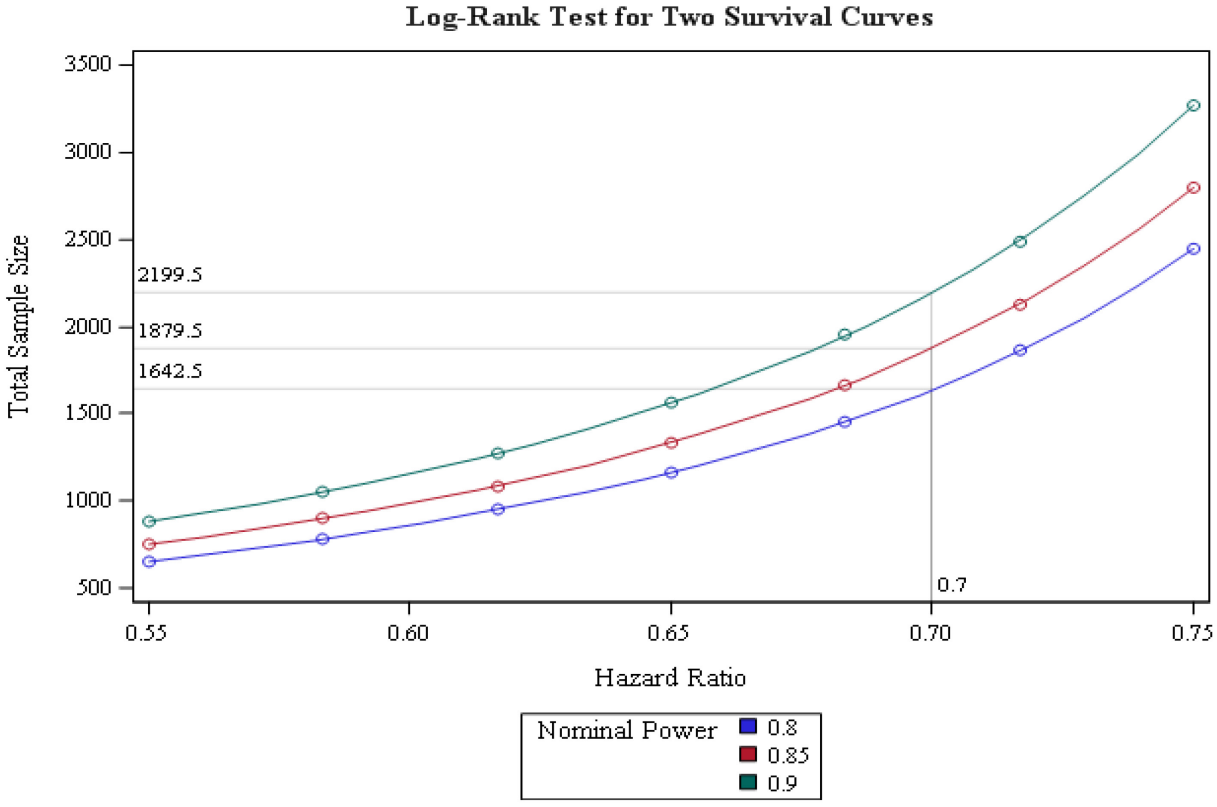
10.5 SAMPLE SIZE

Conservative power calculations are based on symptomatic recurrence rates reported by Rule and colleagues.[49] The following assumptions are incorporated into the power calculation:

1) Unit of randomization: patient
2) Equal randomization ratio (1:1)
3) 15% event rate (composite of USD recurrence) over 2 years in control arm
4) 30% relative risk reduction for intervention arm (HR = 0.7)
5) 20% attrition rate (dropouts, loss to follow up)
6) Two-sided alpha of 0.05, log-rank test for time to event
7) 2 year follow up

N = 821 per arm (total = 1642 study participants) provides 80% power to detect the pre-specified relative risk. Sample size calculations were carried out using SAS (PROC POWER) version 9.4 (SAS Institute Inc., Cary, NC).

Study participants will be recruited from the 4 Clinical Centers over a 2-year period.



10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

Potentially eligible study participants will be identified and screened by interview. Interested study participants will be asked to give informed consent and undergo a screening evaluation to include a complete history, physical examination, and laboratory tests. Females of childbearing potential will undergo pregnancy testing to rule out pregnancy at baseline. Study personnel will assess each study participant against each inclusion and each exclusion criterion, and the Investigator (or designated physician sub-investigator) will determine the study participant's eligibility for study participation. The informed consent process and all assessments will be documented in the study participant's medical record or comparable source document.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Data that may potentially unblind treatment assignment will be handled with special care, so that before unblinding, such data will only be available to:

- SDRC staff who require this data for monitoring, data management and statisicial activities, and safety surveillance
- The clinical center study coordinators who will randomize and interact with both intervention and control arm participants
- The SPS health coaches, who will interact with intervention arm participants who are not meeting their fluid intake goals (see 6.1.3)

Procedures for unblinding an Investigator and/or a participant are included in the study Manual of Procedures and the Statiscial Analysis Plan.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. Accordingly, source documents include, but are not limited to, laboratory reports, radiologist reports and scan images, ultrasound photographs, study participant progress notes, hospital charts, pharmacy records, and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

Regulations require that investigators maintain information in the study participant's research records that corroborate data collected on the eCRF. In order to comply with these regulatory requirements, the

following information will be maintained and made available as required by SDRC monitors and/or regulatory inspectors:

1. Medical history/physical condition of the study participant before involvement in the study sufficient to verify protocol entry criteria.
2. Medical record documenting that informed consent was obtained for the study participant's participation in the study.
3. Dated and signed notes for each in-person study participant visit, including results of examinations.
4. Notations on abnormal laboratory results.
5. Dated printouts or reports of special assessments (eg, 24-hour urine collections).
6. Description of adverse events (AEs) and follow-up of the AEs (minimally, event description, severity, onset date, duration, relation to study drug/device, outcome, and treatment for AE).
7. Notes regarding concomitant medications taken during the study (including start and stop dates).
8. Study participant's condition upon completion of or withdrawal from the study.

12 QUALITY ASSURANCE AND QUALITY CONTROL

NIDDK and their representatives (e.g. SDRC) agree to be responsible for implementing and maintaining quality control and quality assurance systems to ensure that all work incidental to this protocol is conducted and data are generated, documented, and reported in compliance with the protocol; accepted standards of Good Clinical Practice (GCP); and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The clinical center Investigator will provide current copies of the study protocol to all subinvestigators or other site personnel responsible for study conduct.

The SDRC PI will provide the NIDDK with copies of all institutional review board (IRB) actions regarding the study.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

Research will be conducted in compliance with regulations as outlined in 45 CFR part 46 and the ethical framework in the Belmont Report.

13.2 INSTITUTIONAL REVIEW BOARD

The appropriate IRB must approve the protocol and informed consent documents, agree to monitor the conduct of the study, and agree to review study progress periodically, at intervals not to exceed 1 year. The investigator will provide SDRC with documentation that the IRB/EC has approved the study *before* the study may begin.

In addition, the Investigator must provide the following documentation to NIDDK or their representative (e.g., SDRC):

1. IRB annual reapproval of the protocol, per current regulations and current International Conference on Harmonisation guidelines.

2. IRB approval of revisions to the informed consent documents or any amendments to the protocol. The investigator will provide the NIDDK or their representative with documentation of all approvals.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT PROCEDURES AND DOCUMENTATION

The clinical center Investigator has both ethical and legal responsibility to ensure that each study participant being considered for inclusion in this study is given a full explanation of the study. Informed consent will be obtained from all study participants (or their guardian or legally authorized representative [LAR]) before any study-related procedures (including any pretreatment procedures, such as preprocedure sedation) are performed or given.

Informed consent will be documented on an informed consent form (ICF), or through a remote consent process, that has been approved by the same IRB/EC responsible for approval of this protocol. The ICF will conform to FDA regulations in 21 CFR Part 50 and to the institutional requirements for informed consent and applicable regulations. The Investigator agrees to obtain approval from SDRC of any ICF intended for use in the study, before submission for IRB approval.

Consent will be obtained from the participant if age ≥18 years or parent/guardian consent if age < 18 years with adolescent assent, after all questions about study procedures have been addressed.
In addition, age-appropriate assent will be obtained from the pediatric study participants themselves.
Informed consent is an ongoing process that takes place between the Investigator/study staff and study participants. In most cases, this process is initiated with informed consent at the start of the study; however, it also takes place as an ongoing dialogue between the Investigator/study staff and study

participants during the entire duration of their participation. Should the study participants become intolerant of any aspect of the study, their participation will be discontinued.

The approved consent process will be completed with the prospective study study participant or his or her LAR, and the Investigator or qualified designee will be available to answer questions regarding procedures, risks, and alternatives.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

To minimize the chance for serious and unexpected adverse events, study participants will be screened through exclusion criteria for any health conditions that may be exacerbated by participating in this study. Participants are given guidance on when to seek medical attention and a reporting protocol is in place to capture any changes in symptoms with study participation.

A potential risk of this study is a breach of participant confidentiality. We will minimize this risk by linking individual identifying information with participant ID numbers at the site that will only be accessed by the study team in the case of an adverse medical event, participant dropout, or if otherwise deemed necessary by the Investigators.

Due to the financial incentives in this study, we will be collecting Social Security numbers from adult participants so that we can complete W-9 forms for them. Social Security numbers only will be used to generate W-9 forms and will be deleted once they are no longer needed. All adult participants will be asked provide informed consent for use of Social Security numbers for this purpose. We will also collect home addresses to mail incentive payments. Incentive payments will be managed through a University of Pennsylvania-approved partnership between Way to Health and Wells Fargo. Accidental disclosure of Social Security numbers could lead to identity theft. We will use commercial-grade encryption to protect Social Security information in transit. Names and addresses will be stored in encrypted databases. These data will be viewable only by the respective participants, the CC study coordinators, and staff at Way to Health and Wells Fargo.

Adolescent participants will be paid via Clin Card, according to the procedures of their clinical center's institution. Social Security numbers will not be collected in the Way to Health system for adolescents, and their information will not be shared with Wells Fargo.

Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study. Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords. Wherever feasible, identifiers will be removed from study-

related information. Precautions are in place to ensure the data are secure by using passwords and encryption, because the research involves web-based surveys.

Research material will be obtained from patient charts, participant surveys, and from the smart water bottle. All participants will provide informed consent for access to these materials. The data to be collected include demographic data (e.g., age, sex, self-identified race), outcome data, and daily water intake data collected by the smart water bottle. Research material that is obtained will be used for research purposes only. The same procedure used for the analysis of automated data sources to ensure protection of patient information will be used for the survey data, in that patient identifiers will be used only for linkage purposes or to contact study participants. The study identification number, and no other identifying information, will be used on all data collection instruments. All study staff will be reminded to appreciate the confidential nature of the data collected and contained in these databases.

Participation in the proposed study is completely voluntary. The research team will institute strict procedures to maintain confidentiality. All data and records generated during this study will be kept confidential and in accordance with institutional policies and HIPAA on study participant privacy. Study participants will be assigned a unique participant ID number, as mentioned above. The study data will only be shared with the investigative team during the implementation of the study and results will only be presented in aggregate form. Further, study participants and families will have direct access to the study team as a means to voice any questions, concerns, or reservations. Contact information will be provided at the time of consent. Should any specific concerns arise, the study team will intervene to address problems including, if needed, a change or discontinuation of study procedures. The IRB of the appropriate USDRN CC will promptly be informed of any concerns.

The following entities, besides the members of the research team, may receive protected health information (PHI) for this research study: a) Wells Fargo, the company which processes study-related payments. Patient addresses and account balances will be stored on their secure computers. b) P'unk Ave., LLC, a software development company designing the Way to Health website. P'unk Ave. will not store any of the study participants' PHI, but they will have access to de-identified patient information, for the purposes of website administration and development. c) Hidrate Spark, the manufacturer of the smart water bottle that will be used in the study. d) Twilio, Inc., the company which processes some study-related messages. Twilio will store study participants' phone numbers on their secure computers. e) the SDRC which manages the EDC database and performs study management and monitoring. f) IBM Clinical which hosts the EDC database server. g) the central laboratory at University of Texas Southwestern, which performs the 24-hour urine testing. h) the Institutional Review Boards and offices for Human Research Protections at the SDRC and each Clinical Center. i) Federal and state agencies (for example, the Department of Health and Human Services, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

The research use of stored identified or coded specimens or data, when researchers can identify the sources, must receive prospective and continuing IRB review and approval. This includes research protocols where the remaining research activities are limited to data analyses, and the subsequent research use of specimens or data previously collected under now-terminated protocols.

13.5 FUTURE USE OF STORED SPECIMENS

Specific consent is required for biological samples to be stored for future studies. Study participants who consent to such storage of samples will be asked to follow the site's IRB-approved process to document their consent. Participation in the study is not contingent upon a study participant's agreement to provide additional biological samples.

Once the appropriate essential information has been provided to the study participant and fully explained by the investigators or qualified designee, and it is felt that the study participant understands the implications of participating, the study participant and the investigator or designee will sign and date the institutional review board (IRB)/ethics committee (EC)-approved written ICF or complete the IRB-approved remote consent process. If a paper ICF was signed, the study participant will receive a copy of the signed ICF; the original signed and dated ICF will be kept in the site's regulatory file. Documentation of the study participant's informed consent for and participation in this trial will be noted in the study participant's medical record.

The study participant or his or her LAR will be informed in a timely manner if new information becomes available that may be relevant to the study participant's willingness to continue participation in the trial. The communication of this information to the study participant will be documented.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Study sites will transcribe study participant source data, or directly enter required data, into eCRFs using a computerized electronic data capture (EDC) system. The EDC system is managed by the SDRC, and is compliant with all relevant aspects of GCP. Edit checks, electronic queries, and audit trails are built into the system to ensure accurate and complete data collection.

Protocol-specified source documents (eg, hospital discharge summaries, operative/procedural reports, and other source documents, as applicable) will be retrieved as necessary. Copies of all study-related documentation will be retained at the site.

Periodic data quality checks will be performed to ensure appropriate data recording. The database will be restricted to only authorized users and will be password-protected. Individual user accounts with passwords will be used to restrict access. A network firewall will be used to prevent unauthorized

external use. Data will be stored on encrypted, password-protected servers and backed up regularly through the SDRC, located at Duke Clinical Research Institute.

14.2 STUDY RECORDS RETENTION

The clinical center Investigator will maintain the records of final eCRFs, worksheets, and all other study-specific documentation (eg, source documentation) until notified by the NIDDK or SDRC that records may be destroyed. To avoid error, the Investigator will contact the SDRC before the destruction of any records pertaining to the study to ensure they no longer need to be retained. In addition, SDRC will be contacted if the PI plans to leave the institution so that arrangements can be made for the transfer of records.

The Investigator will not dispose of any records relevant to this study without either (1) obtaining written permission from the NIDDK or (2) providing an opportunity for the NIDDK to collect such records. The Investigator takes responsibility for maintaining adequate and accurate source documents of all observations and data generated during this study. Such documentation is open to inspection by the sponsor, their representatives, as well as the NIH, and other regulatory agencies, as provided by law.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the investigational plan or the Investigator Agreement.

Investigators are required to obtain approval from the SDRC PI or their designated delegate, and their IRB, before initiating deviations from the investigational plan or protocol, except where necessary to protect the life or physical well-being of a study participant in an emergency. Such approval will be documented in writing and maintained in study files. Preapproval is generally not expected in situations where unforeseen circumstances are beyond the investigator's control, (eg, study participant did not attend scheduled follow-up visit, blood sample lost by laboratory); however, the event is still considered a deviation.

Deviations will be reported to SDRC regardless of whether medically justifiable, or taken to protect the study participant in an emergency. See the Manual of Procedures for detailed information on reporting deviations.

The IRB/EC will be informed of all protocol changes by the sponsor or the investigator in accordance with applicable regulations and the IRB/EC's established procedures. No deviations from the protocol of any type will be made without complying with all the IRB/EC's established procedures.

Investigators will maintain documentation of the dates and reasons for each deviation from the protocol.

14.4 PUBLICATION AND DATA SHARING POLICY

The USDRN will be operating under the NIDDK Data Sharing Policy. (*https://www.niddk.nih.gov/research-funding/process/human-subjects-research/Documents/PublicversionNIDDKdatasharingpolicy2013July2013.pdf*). This policy seeks maximal benefit from the data and samples collected from multi-center clinical studies in which the NIDDK has invested substantial resources, and study investigators and participants have invested substantial effort. NIDDK has established repositories for study data, and biologic and genetic samples to foster the use of these resources. The policy was established to balance the interest of the study investigators with those of the larger scientific research community by setting a defined period of exclusive access by study investigators; after that time data will become "publicly" available through the NIDDK Data Repository.

15 CONFLICT OF INTEREST POLICY

A USDRN financial disclosure guideline has been developed to promote fair, open, and unfettered discussion of important conflict of interest concerns that often emerge during the design and conduct of multicenter clinical trials. The aim is to ensure that the scientific design, conduct, and reporting of the study are not biased by financial influences. The USDRN guideline does not supersede Institutional requirements developed to comply with Public Health Service (PHS) regulations on Financial Conflict of Interest reporting. This guideline requires Principal Investigators and other active participants in study design and conduct, such as committee members, subcontractors, or other regular attendees at Steering Committee meetings to fully disclose all commercial or professional ties that might pose a real or perceived conflict of interest. Oversight of reported conflict disclosures will be managed by the Executive Committee.

16 LITERATURE REFERENCES

1. Scales CD, Jr., Smith AC, Hanley JM, Saigal CS. Prevalence of Kidney Stones in the United States. Eur Urol 2012.
2. Litwin MS, Saigal C. Urologic Diseases in America. In: Services UDoHaH, ed. Washington, DC: US Government Printing Office; 2012.
3. Fwu CW, Eggers PW, Kimmel PL, Kusek JW, Kirkali Z. Emergency department visits, use of imaging, and drugs for urolithiasis have increased in the United States. Kidney Int 2013;83:479-86.
4. Borghi L, Meschi T, Amato F, Briganti A, Novarini A, Giannini A. Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. J Urol 1996;155:839-43.
5. Lotan Y, Buendia Jimenez I, Lenoir-Wijnkoop I, et al. Increased water intake as a prevention strategy for recurrent urolithiasis: major impact of compliance on cost-effectiveness. J Urol 2013;189:935-9.
6. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. N Engl J Med 1993;328:833-8.

7. Frank M, De Vries A. Prevention of urolithiasis. Education to adequate fluid intake in a new town situated in the Judean Desert Mountains. Arch Environ Health 1966;13:625-30.
8. Parks JH, Goldfischer ER, Coe FL. Changes in urine volume accomplished by physicians treating nephrolithiasis. J Urol 2003;169:863-6.
9. Jackson E. Between a Rock and a Hard Place: Getting Families to Change Behaviors to Reduce Pediatric Stone Disease Recurrence. J Urol 2014;192:1324-5.
10. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. J Urol 2014;192:316-24.
11. Qaseem A, Dallas P, Forciea MA, Starkey M, Denberg TD, Clinical Guidelines Committee of the American College of P. Dietary and pharmacologic management to prevent recurrent nephrolithiasis in adults: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2014;161:659-67.
12. Volpp KG, Gurmankin Levy A, Asch DA, et al. A randomized controlled trial of financial incentives for smoking cessation. Cancer Epidemiol Biomarkers Prev 2006;15:12-8.
13. Volpp KG, Troxel AB, Pauly MV, et al. A randomized, controlled trial of financial incentives for smoking cessation. N Engl J Med 2009;360:699-709.
14. Halpern SD, French B, Small DS, et al. Randomized trial of four financial-incentive programs for smoking cessation. N Engl J Med 2015;372:2108-17.
15. Higgins ST, Bernstein IM, Washio Y, et al. Effects of smoking cessation with voucher-based contingency management on birth outcomes. Addiction 2010;105:2023-30.
16. Volpp KG, John LK, Troxel AB, Norton L, Fassbender J, Loewenstein G. Financial incentive-based approaches for weight loss: a randomized trial. JAMA 2008;300:2631-7.
17. John LK, Loewenstein G, Troxel AB, Norton L, Fassbender JE, Volpp KG. Financial incentives for extended weight loss: a randomized, controlled trial. J Gen Intern Med 2011;26:621-6.
18. Forster JL, Jeffery RW, Sullivan S, Snell MK. A work-site weight control program using financial incentives collected through payroll deduction. J Occup Med 1985;27:804-8.
19. Jeffery RW, Forster JL, Snell MK. Promoting weight control at the worksite: a pilot program of self-motivation using payroll-based incentives. Prev Med 1985;14:187-94.
20. Vandrey R, Bigelow GE, Stitzer ML. Contingency management in cocaine abusers: a dose-effect comparison of goods-based versus cash-based incentives. Exp Clin Psychopharmacol 2007;15:338-43.
21. Higgins ST, Budney AJ, Bickel WK, Foerg FE, Donham R, Badger GJ. Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. Arch Gen Psychiatry 1994;51:568-76.
22. Silverman K, Wong CJ, Higgins ST, et al. Increasing opiate abstinence through voucher-based reinforcement therapy. Drug Alcohol Depend 1996;41:157-65.
23. Volpp KG, Loewenstein G, Troxel AB, et al. A test of financial incentives to improve warfarin adherence. BMC Health Serv Res 2008;8:272.
24. Kimmel SE, Troxel AB, Loewenstein G, et al. Randomized trial of lottery-based incentives to improve warfarin adherence. Am Heart J 2012;164:268-74.
25. Priebe S, Bremner SA, Lauber C, Henderson C, Burns T. Financial incentives to improve adherence to antipsychotic maintenance medication in non-adherent patients: a cluster randomised controlled trial. Health Technol Assess 2016;20:1-122.
26. Skinner BF. Cumulative Record: A selection of papers. 3rd ed. New York: Meredith; 1972.
27. Bigelow GE, Silverman K. Theoretical and Empirical Foundations of Contingency Management Treatments for Drug Abuse. In: Higgins ST, Silverman K, eds. Motivating Behavior Change Among Illicit Drug Users. Washington, DC: American Psychological Association; 1999:15-30.
28. Sorsdahl K, Myers B, Ward CL, et al. Adapting a blended motivational interviewing and problem-solving intervention to address risky substance use amongst South Africans. Psychother Res 2015;25:435-44.

29. Hill-Briggs F, Gemmell L. Problem solving in diabetes self-management and control: a systematic review of the literature. Diabetes Educ 2007;33:1032-50; discussion 51-2.
30. Gross R, Bellamy SL, Chapman J, et al. Managed problem solving for antiretroviral therapy adherence: a randomized trial. JAMA Intern Med 2013;173:300-6.
31. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA 1991;265:3255-64.
32. Seekles W, van Straten A, Beekman A, van Marwijk H, Cuijpers P. Stepped care for depression and anxiety: from primary care to specialized mental health care: a randomised controlled trial testing the effectiveness of a stepped care program among primary care patients with mood or anxiety disorders. BMC Health Serv Res 2009;9:90.
33. Saint S, Greene MT, Krein SL, et al. A Program to Prevent Catheter-Associated Urinary Tract Infection in Acute Care. N Engl J Med 2016;374:2111-9.
34. Sarica K, Inal Y, Erturhan S, Yagci F. The effect of calcium channel blockers on stone regrowth and recurrence after shock wave lithotripsy. Urol Res 2006;34:184-9.
35. Fink HA, Akornor JW, Garimella PS, et al. Diet, fluid, or supplements for secondary prevention of nephrolithiasis: a systematic review and meta-analysis of randomized trials. Eur Urol 2009;56:72-80.
36. Loewenstein G, Brennan T, Volpp KG. Asymmetric paternalism to improve health behaviors. Jama 2007;298:2415-7.
37. Loewenstein G, Asch DA, Volpp KG. Behavioral economics holds potential to deliver better results for patients, insurers, and employers. Health Aff (Millwood) 2013;32:1244-50.
38. Zeelenberg M, Beattie J, van der Pligt J, de Vries N. Consequences of regret aversion: Effects of expected feedback on risky decision making. Organizational Behavior & Human Decision Processes 1996;65:148-58.
39. Zeelenberg M, Pieters R. Consequences of regret aversion in real life: The case of the Dutch postcode lottery. Organizational Behavior & Human Decision Processes 2004;93:155 - 68.
40. Chapman GB, Coups EJ. Emotions and preventive health behavior: worry, regret, and influenza vaccination. Health Psychol 2006;25:82-90.
41. Patel MS, Asch DA, Volpp KG. Use of wearable monitoring devices to change health behavior--reply. JAMA 2015;313:1865-6.
42. Kalbfleisch JD, Prentice RL. The statistical Analysis of Time Failure Data. 2nd ed. New York, NY: John Wiley & Sons; 2002.
43. Cox D. Regression models and life-tables (with discussion). J Royal Statist Soc B 1972;1972:187-220.
44. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Statist Assn 1958:457-81.
45. Anderson PK, Gill RD. Cox's regression model for counting processes: a large sample study. Annals of Statistics 1982;10:1100-20.
46. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-Effectiveness in Health and Medicine. New York: Oxford University Press; 1996.
47. Reed SD, Li Y, Kamble S, et al. Introduction of the Tools for Economic Analysis of Patient Management Interventions in Heart Failure Costing Tool: a user-friendly spreadsheet program to estimate costs of providing patient-centered interventions. Circ Cardiovasc Qual Outcomes 2012;5:113-9.
48. Fann C, Huang P, Yen AM, Chen H. Patient Utility Measurement for Managing Ureteral Stones: A Modified Standard Gamble Approach. Value Health Regional Issues 2012;1:87-92.
49. Rule AD, Lieske JC, Li X, Melton LJ, 3rd, Krambeck AE, Bergstralh EJ. The ROKS nomogram for predicting a second symptomatic stone episode. J Am Soc Nephrol 2014;25:2878-86.

APPENDIX

Comprehensive Assessment of Self-Reported Urinary Symptoms